CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020351/S01/S03

MEDICAL REVIEW(S)

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SEP 17 1997

NDA 20-351 / Pediatric Supplement
VISIPAQUE (iodixanol) Injection

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SEP 17 1997

NDA 20-351 (Pediatric Supplement)
Drug Name: Visipaque (iodixanol injection)
New Indications: Pediatric Cardioangiography, Head/Body CT Scans, and Excretory Eurography

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Reviewer's Overall Summary

This was a phase-3. double-blind, randomized, parallel group, multicenter, clinical trials was conducted to compare the safety and efficacy of Visipaque and Omnipaque (at an iodine concentration of 270, 320 mgI/mL versus Omn-300 and 350 mgI/mL, repectively) in pediatric patients with known or highly suspected cardio-renal pathology.

Eight (8) double-blind, comparative clinical trials in four pediatric intravascular indications were conducted in United States and European trials. Three (39998-013, 39998-011, 39998-012) in U. S. and five (DXV036, DXV039, DXV038, DXV037, DXV041) in European clinical trials. One additional pediatric phase-1 pharmacokinetic study (39998-018) was conducted with Visipaque 320 mgI/mL in the United States. In all of the doses studied Visipaque (iodixanol) as demonstrated in newborn infants <months of age, the half-life was estimated approximately 4.1 hours. Children <12 years of age, the half-life of iodixanol was estimated 2.3 hours (approximately that of adults with normal renal function 2.1 hours).

A total of 694 (378 males and 316 females) patients including one phase-1 trial was studied in this NDA submission: Two hundred seven-one (153 males & 118 females) patients were enrolled in the U.S clinical trials versus 380 (198 males and 182 females) in the European clinical trials. In the controlled clinical trials, 416 (225 males and 191 females) patients received Visipaque 270 mgI/mL, 320 mgI/mL, and 235 (126 males and 109 females) patients received Omnipaque 300 mgI/mL, 350 mgI/mL, respectively. Four hundred fifty-nine (459) pediatric patients (252 males and 207 females) received Visipaque and 235 (126 males and 109 females) patients received Omnipaque. None of the patients in this study were excluded or withdrawn from the analysis, except for four patients who did not received a dose.

Demographics/Dosages - Demongraphic and dosage information are summarized in Table a-e, and no significant differences were noted between drug groups within centers and between U. S. and non-U. S. centers. The demographic profiles were predominantly Caucasian (83% in the Vis-270 group, 75% in the Vis-320 group and 81% in the Omnipaque group) and included a range of ages from for angiocardiography, years for CT scanning of the head, for CT scanning of the body and for excretory urology. Race, however, appears to be unevenly distributed.

Dosage profiles - There were no significant differences between drug groups. Children and especially very young children cannot be considered as small adults because of pharmacokinetic differences, different pharmacodynamic responses, specific age-related vulnerability and specific pathology. The iodine concentration and injection volume as used with Visipaque in the phase-3 clinical trials were similar to those with the other non-ionic radiocontrast agents used. Visipaque-320 causes smaller disturbances in cardiovascular function than do other contrast agents.

The proposed clinical dose levels are as follows:

Dose and Route of Administration - intravascular (IA & IV) administrations.

Intraarterial Injection - The recommended pediatric angiocardiography dose of Visipaque 320 mgI/mL (by age group):

Intra-arterial Injection Site	0 to <29 days	29 days to < 2 years	2 to 12 years
Aorta	1-6 mL	4-15 mL	5-50 mL
Pulmonary artery	4-5 mL	5-20 mL	5-35 mL
Right and left ventricle	1-9 mL	2-24 mL	13-50 mL
Total Dose Per Patient (Not to exceed)	5 mL/kg (10 mL/kg, or 30 mL)	5 mL/kg (10 mL/kg, or 100 mL)	5 mL/kg (10 mL/kg, or 200 mL)

Intravenous Injection - The recommended doses of Visipaque 270 and/or Visipaque 320 mgI/mL for all intravenous indications are summarized below:

Procedure	Visipaque 270	Visipaque 320	Maximum Total Dose
CT Scan Of Head	1-3 mL/kg	1-3 mL/kg	Not to exceed 3 mL/kg
CT Scan Of Body	1-3 " "	1-3 " "	" " "
Excretory Urography	1-3 " "	1-3 " "	" " "

Dose response - A lower dose of Visipaque-270 mgI/mL demonstrated imaging effectiveness similar to that of comparably lower dose of Omnipaque-300 mgI/mL and higher dose of Visipaque-320 mgI/mL. .

Pre-medication - A total of 113 of the 296 patients (38%) in these clinical trials was sedated prior to the CT scanning; these patients included: 34 of the 96 patients (35%) in the Vis-270 mgI/mL, 41 of the 100 patients (41%) in the Vis-320 mgI/mL and 38 of the 100 patients (38%) in the Omn-300 group. The three groups were comparable with respect to the most common premedication. Across all three groups of the four trials, the most commonly used medications were psycholeptics and anesthetics. No statistically significant differences between drug groups.

Premedication Given	CT of the Head		CT of the Body		Total
Study Centers	39998-011	DXV039	39998-012	DXV038	4
Number of patients	75	75	79	67	296
Vis-270 mgI/mL	7/23 (31%)	8/25 (32%)	10/26 (38%)	9/22 (41%)	34/96 (35)
Vis-320 mgI/mL	11/27 (41%)	11/25 (44%)	8/26 (31%)	11/22 (50%)	41/100(41)
Omn-300 mgI/mL	10/25 (40%)	10/25 (40%)	11/27 (41%)	7/23 (30%)	38/100(38)
	28/75 (37%)	29/75 (38%)	29/79 (37%)	27/69 (39%)	113/296(38)

A study by Allen Mitchell et al, suggests that the life-threatening reactions were seen in children sedated prior to CT scans at a rate four times higher than that of the remaining population.

He cautioned, that sedated children should be kept under intense observation before, during and after scans to avoid the possibility of severe reaction leading to long term effects or deaths (note; there are no indications that CT itself is involved in the reactions). In the current submission, however, no conclusion can be made. The sponsor has been informed that subset analysis should be provided.

Safety - Safety was assessed by measuring vital signs, blood biochemical, hematological parameters, ECGs, neurological examinations and adverse events.

Vital Signs - There were no significant differences between Visipaque and Omnipaque in vital signs measured after the intravascular administration in either the U. S. or European comparative trials. Although there were a few minor increases and/or decreases in vital sign parameters, no clinically significant trends observed.

Laboratory Parameters - No clinically significant mean changes in blood chemistry or hematological parameters were observed for
contrast agents administration. Individual changes in specific parameters, when occurring, were similar in magnitude and frequency for both contrast agent groups. Most abnormal laboratory values were not clinically relevant and returned
There were no clinically meaningful trends observed in laboratory parameters following Visipaque administration. ECGs - There were no clinically significant differences observed in either individual percent changes from baseline in RR, PR, corrected QT intervals, ST segment or T-wave amplitude among injection sites within each group. The incidence of arrhythmia for each trial, and for all trials combined by group and stratified by age-group, recorded 20 patients in the Vis-320 group and 8 patients in the Omn-350 group that experienced at least one post-injection arrhythmia. The most frequently recorded type of arrhythmia in both groups was premature ventricular contraction (PVC) after LV injection.

Deaths - Death during and/or after the angiographic procedure occurred in five (1%) of 459 Visipaque patients and in one (0.5%) of 235 Omnipaque patients. Deaths within 25 days of post-contrast administration occurred in five angiocardiography patients (4 in the Visipaque group, 1 in the Omnipaque group) and one in the Visipaque-320 group following CT scanning of the body. It seems that a few more deaths occurred in the Visipaque group than in the Omnipaque group. None of the deaths were considered related to either study drug as stated by the investigator.

Adverse Events other than life-threatening - With respect to drug tolerance, two serious adverse effects (acute renal failure) were encountered one in each drug group. Four hundred fifty-six patients who received Vis-320 and Vis-270 mgI/mL combined and 235 patients who received Omn-350 & Omn-300 mgI/mL combined experienced a total of 108 and 34 adverse events, respectively. The most frequently occurring adverse events were Arrhythmia (4.8%), vomiting (3.5%), nausea (2.0%), Fever (1.8%), Pruritus (>1%) and the Others (<1%).

There were no statistical significant differences between drug groups. Note: The incidence of adverse events was much greater in the Visipaque group than in the Omnipaque group. Similarily, there were higher incidence of adverse effects in the intraarterial trials than in the intravenous trials.

Efficacy - The overall quality of radiographic visualization was comparable between Visipaque and Omnipaque both in the United States and European clinical trials. The contrast agents provided good/excellent quality of visualization from for the Visipaque patients versus with the Omnipaque patients. With respect to effectiveness issue, however, there is no major ground for disapproval. Following the FDA Medical Imaging Drug Advisory Committee Meeting dated May 27, 1993, however, the Agency has adapted a new policy that approves efficacy on any new iodinated contrast agents with indications that fall within the dose ranges, concentration of iodine, osmolality and viscosity.

Visipaque (Iodixanol) is a new non-ionic, dimeric, hexaiodinated, water-soluble radiocontrast agent developed by Nycomed AS, Norway. At iodine-equivalent concentrations, the osmolality of iodixanol solution is less than half that of solutions of non-ionic monomeric contrast agents such as Omnipaque. Currently, a number of marketed products similar to that above have been approved for intravascular and non-intravascular use in various radiographic procedures. They are the following:

The Physical Properties of the Following Contrast Media

GENERIC NAME	TRADE NAME (MANUFACT)	CONC. (mgI/mL)	MOLECULAR WEIGHT	OSMOLALITY (m0smol/kg H_20)	VISCOSITY(cP) (37°C)
iohexol	Omnipaque(Nycomed)	350	821	845	10.4
		300		690	6.1
		240		520	3.4
		210		460	2.5
		140		322	1.5
iodixanol	Visipaque (Nycomed)	320	1550	290	11.8
		270		290	6.3
iopamidol	Iopamiro (Bracco)	350	777	785	8.4
		300		616	4.7
		250		524	3.0
		128		290	1.4
iopromide	Ultravist (Berlex)	370	791	774	10.0
		300		607	4.9
		240		483	2.8
		150		328	1.5
ioversol	Optiray(Mallinckrodt)	350		792	9.0
		320		702	5.8
		240		502	3.0
		160		355	1.9
iotrolan	Isovist (Berlex)	280	1626	295	6.3
ioxilan	Ioxitol (Cook Imaging)	350	791	690	8.1
		300		585	5.1

Post-marketing Experience:

Visipaque (iodixanol) has been approved for adults intravascular indications in Australia, Bulgaris, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Israel, Luxembourg, Netherlands, Norway, Romania, Russia, Spain, Sweden, Switzerland & the United Kingdom. Visipaque has not been withdrawn for any reason.

Labeling Review - The labeling meets the requirements of the regulations with regard to style, format and content. It is acceptable but we suggest the following changes (a draft labeling attached):

Summary - Based on the data submitted, The Reviewer believes the results of this study supports the claim that Visipaque is comparable to Omnipaque for pediatric intravascular use (4 indications). Since these agents are used in the same dosage form by the same route of administration, in the approved dosage range, there is no problem with safety or untoward adverse reactions. This application may be approved on the basis of paragraphs 201.57(f)(9)(ii) through (f)(9)(v) of this section including sufficient similarilty to permit extrapolation to pediatric populations on adult efficacy and safety data.

Recommendation - The Reviewer recommends that this NDA-supplement is approvable pending labeling revision.

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Silas Chow, M. D.
MOR

c.c.
Orig - NDA-supplement
HFD - 160/Div File
HFD - 160/MOR/SChow, M.D./May 22, 1997
HFD - 160/CSO/SCusack
R/D - Init. By A. Eric Jones, M. D. (Term Leader)

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DIVISION OF MEDICAL IMAGING & PHARMACEUPTICAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW OF NDA SUPPLEMENT
PEDIATRIC PHASE-4 CLINICAL STUDIES

NDA 20-351
Visipaque® (Iodixanol Injection)
Nycomed Inc.
Wayne, PA 19087-8630

Document Date: October 10, 1996
Date Assigned: November 1, 1996
Date Completed: May 22, 1997
Silas Chow, M. D MOR

Type of Supplement: **Pediatric New Indications**

BACKGROUND:

Visipaque® (iodixanol) Injection, is a dimeric, nonionic water-soluble, radio-contrast agent. Sterling Winthrop conducted eighteen clinical trials in adults with iodixanol in the United States under which was submitted on March 19, 1990. On 04, October 1994, Nycomed purchased the imaging business of Sterling and IND ownership was subsequently transferred to Nycomed Inc. Visipaque® (iodixanol) has been approved on March 22, 1996 by the United States Food and Drug Administration for a variety of contrast medium examinations which include intravascular uses in adults; in angiocardiography (320 mgI/mL), cerebral arteriography (320 mgI/mL), CT of the head (270 and 320 mgI/mL), CT of the body (270 and 320 mgI/mL), visceral angiography (270 and 320 mgI/mL), peripheral arteriography (320 mgI/mL), urography (270 and 320 mgI/mL) and venography (270 mgI/mL).

The current supplemental New Drug Application provides for an additional intravascular indications for pediatric cardioangiography, pediatric CT of the head/body and pediatric excretory urography and has not previously been submitted to the United States Food and Drug Administration in support of other indications.

INDICATION	CONCENTRATIONS (mgI/mL) Iodixanol		Iohexol
Angiocardiography		320	350
CT of the Head	270	320	300
CT of the Body	270	320	300
Excretory Urography	270	320	300

Eight (8) double-blind, randomized, comparative clinical trials in four pediatric intravascular indications were conducted comparing Visipaque 270 mgI/mL, 320 mgI/mL and Omnipaque 300 mgI/mL, 350 mgI/mL in three (39998-013, 39998-011, 39998-012) United States clinical trials, and comparing Visipaque 270 mgI/mL, 320 mgI/mL versus Omnipaque 300 mgI/mL, 350 mgI/mL in five (DXV036, DXV039, DXV038, DXV037, DXV041) European clinical trials. One additional non-comparative phase-1 pharmacokinetic study (#2493) was performed for 43 pediatric patients (27 males and 16 females) in United States.

A total of 694 (378 males and 316 females) patients including one phase-1 trial were studied in this NDA submission; Two hundred seventy-one (153 males & 118 females) patients were enrolled in the U.S clinical trials versus 380 (198 males and 182 females) in the European clinical trials. In the controlled clinical trials, 416 (225 males and 191 females) patients received Visipaque 270 mgI/mL, 320 mgI/mL, and 235 (126 males and 109 females) patients received Omnipaque 300 mgI/mL, 350 mgI/mL, respectively. Four hundred fifty-nine (459) pediatric patients (252 males and 207 females) received Visipaque and 235 (126 males and 109 females) patients received Omnipaque. No patients in this study were excluded or withdrawn from the analysis, except four patients which were not dosed.

A phase-1 trial (39998-018) was conducted in the U.S. to evaluate the pharmacokinetics of Vis-320 mgI/mL in pediatric patients from newborn to <12 years of age. Eight phase-3, double-blind, randomized, parallel-group trials comparing the safety and effectiveness of Vis-270, 320 mgI/mL to that of Omn-300, and 350 mgI/mL were studied in pediatric patients from newborn to <18 years of age. The patient disposition for all trials combined by inidcation as follows:

Indications	Phase-1 Visipaque	Phase-3 Visipaque	Phase-3 Omnipaque	Total
Cardioangiography	41	120	85	246
CT scanning of Head	2	100	50	152
CT scanning of Body	-	96	50	146
Excretory Urography	-	100	50	150
Total	43	416	235	694

Dose and Route of Administration - intravascular (IA & IV) administrations.

Intraarterial Injection - The recommended pediatric angiocardiography dose of Visipaque 320 mgI/mL (by age group):

Intra-arterial Injection Site	0 to <29 days	29 days to < 2 years	2 to 12 years
Aorta	1-6 mL	4-15 mL	5-50 mL
Pulmonary artery	4-5 mL	5-20 mL	5-35 mL
Right and left ventricle	1-9 mL	2-24 mL	13-50 mL
Total Dose Per Patient (Not to exceed)	5 mL/kg (10 mL/kg, or 30 mL)	5 mL/kg (10 mL/kg, or 100 mL)	5 mL/kg (10 mL/kg, or 200 mL)

Intravenous Injection - The recommended doses of Visipaque 270 and/or Visipaque 320 mgI/mL for all intravenous indications are summarized below:

Procedure	Visipaque 270	Visipaque 320	Maximum Total Dose
CT Scan Of Head	1-3 mL/kg	1-3 mL/kg	Not to exceed 3 mL/kg
CT Scan Of Body	1-3 " "	1-3 " "	" " "
Excretory Urography	1-3 " "	1-3 " "	" " "

Note: Children normally receive relatively higher doses of radio-contrast agent than adults (dose/kg bw), from a physiological and pathological standpoint.

A summary of U.S. studies for Phase-1 protocol (39998-018) pharmacokinetics and Phase-3 eight clinical trials (3 U. S. and 5 European) are presented in the Table attached. Both Demographic Characteristics and Dosage Information by age group are also presented in the Table attached.

Table 2.3A
Phase I, Open-Label, Pharmacokinetic and Safety Trial in Pediatric Patients Referred for Contrast-Enhanced Diagnostic Procedures [a]

Trial No. [Report No.]	Country No. of Sites [Start Date-End Date]	Contrast Agent-mgI/mL (Lot No.)	N/n [b] (M/F)	Age Mean (Range)	Total Injection, Mean (Range)		SNDA Location (Vol:Pg)	
					Volume (mL)	Dose (gI)	Full Report, Data Listings	Case Report Forms
39998-018 [2493]	United States 9 [c] [April 1995 - December 1995]	VIS-320 (R003KL)	43/43 [a] (27/16)	1.87 yr	37.4	12.0	3:1-388 4:1-372 6:1-396 7:1-372	3:125-155 6:133-163

[a] Of the 43 patients studied, 41 underwent angiocardiographic procedures and are included in the intraarterial data in the integrated summary of safety (ISS) and 2 underwent computed tomography (CT) scanning of the head or neck and are included in the intravenous and CT head data in the ISS.

[b] N=number of patients enrolled/randomized; n=number of patients evaluable for safety. Numbers for males (M) and females (F) include only those evaluable for safety.

[c] Although nine trial sites were initiated, only seven trial sites enrolled patients.

REF: Trial Report 2493 (Trial 39998-018)

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Table 2.3B
Intraarterial Administration: Summary of Completed Phase III Pediatric Clinical Trials

Trial No. [Report No.]	Country No. of Sites [Start Date-End Date]	Contrast Agent-mgI/mL (Lot No.)	N/n [a] (M/F)	Age Mean (Range)	Total Injection, Mean (Range) Volume (mL)	Dose (gI)	SNDA Location (Vol:Pg) Full Report, Data Listings	Case Report Forms
Phase III Angiocardiography Controlled, Double-Blind, Randomized, Parallel-Group Trials (Nonionic Contrast Agent Comparator)								
39998-013 [1968]	United States 7 [January 1994-October 1995]	VIS-320 (R003KL)	58/58 (30/28)	2.14 yr	49.8	15.95	9:1-434 10:1-438	9:157-199
		OMN-350 (R002KL)	60/59 (30/29)	2.07 yr	42.3	14.80	11:1-411 12:1-327	
DXV036 [2509]	Belgium 2 [March 1994-July 1995]	VIS-320 (303037)	62/62 [b] (30/32)	3.45 yr	52.5	16.79	13:1-383 14:1-405	15:295-328
		OMN-350 (309002)	26/26 (15/11)	4.63 yr	61.3	21.47	15:1-366 16:1-131	

[a] N=number of patients enrolled/randomized; n=number of patients evaluable for safety. Numbers for males (M) and females (F) include only those evaluable for safety.

[b] Includes 10 'pilot' patients who received VIS-320 in an open Phase II portion of the trial and who were evaluable for safety.

REF: Trial Reports 1968 (Trial 39998-013) and 2509 (Trial DXV036)

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Table 2.3C
Intravenous Administration: Summary of Completed Phase III Pediatric Clinical Trials

Trial No. [Report No.]	Country No. of Sites [Start Date-End Date]	Contrast Agent-mgI/mL (Lot No.)	N/n [a] (M/F)	Age Mean (Range)	Total Injection, Mean (Range)		SNDA Location (Vol:Pg)	
					Volume (mL) Mean (Range)	Dose (gI) Mean (Range)	Full Report, Data Listings	Case Report Forms
Phase III Computed Tomography Scanning of the Head Controlled, Double-Blind, Randomized, Parallel-Group Trial (Nonionic Contrast Agent Comparator)								
39998-011 [1966]	United States 6 [January 1994-June 1995]	VIS-270 (R002KN, R008HP)	23/23 (14/9)	5.82 yr	39.4	10.64	18:109-364 19:1-375 20:1-212	18:229-247
		VIS-320 (R003KL)	27/27 (16/11)	5.66 yr	44.6	14.27		
		OMN-300 (R001KL, R009LE)	25/25 (19/6)	5.87 yr	45.5	13.64		
DXV039 [2512]	Sweden 1 [May 1994-April 1995]	VIS-270 (312000)	25/25 (11/14)	8.43 yr	89.1	24.06 (5.94-40.50)	21:1-325	21:261-283
		VIS-320 (309107)	25/25 (15/10)	8.76 yr	89.7	28.70		
		OMN-300 (311107)	25/25 (12/13)	8.09 yr	84.8	25.45		

[a] N=number of patients enrolled/randomized; n=number of patients evaluable for safety. Numbers for males (M) and females (F) include only those evaluable for safety.

REF: Trial Reports 1966 (Trial 39998-011) and 2512 (Trial DXV039)

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Table 2.3C
Intravenous Administration: Summary of Completed Phase III Pediatric Clinical Trials

Trial No. [Report No.]	Country No. of Sites [Start Date-End Date]	Contrast Agent-mgI/mL (Lot No.)	N/n [a] (M/F)	Age Mean (Range)	Total Injection, Mean (Range)		SNDA Location (Vol:Pg)	
					Volume (mL) Mean (Range)	Dose (gI) Mean (Range)	Full Report, Data Listings	Case Report Forms
Phase III Computed Tomography Scanning of the Body Controlled, Double-Blind, Randomized, Parallel-Group Trial (Nonionic Contrast Agent Comparator)								
39998-012 [1967]	United States 7 [February 1994-December 1994]	VIS-270 (R002KN, R008HP)	26/26 (16/10)	5.19 yr	37.4	10.09	22:1-397 23:1-519	22:123-139
		VIS-320 (R003KL)	26/26 (14/12)	4.87 yr	35.1	11.24		
		OMN-300 (R001KL, R009LE)	27/27 (14/13)	5.56 yr	40.1	12.04		
DXV038 [2511]	Norway 1 [May 1994-October 1995]	VIS-270 (312001)	22/22 (14/8)	4.79 yr	37.9	10.24	24:124-372 25:1-302	25:261-281
		VIS-320 (309108)	22/22 (14/8)	4.85 yr	37.4	11.96		
		OMN-300 (311106)	23/23 (11/12)	5.21 yr	39.2	11.77		

[a] N=number of patients enrolled/randomized; n=number of patients evaluable for safety. Numbers for males (M) and females (F) include only those evaluable for safety.
REF: Trial Reports 1967 (Trial 39998-012) and 2511 (Trial DXV038)

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Table 2.3C
Intravenous Administration: Summary of Completed Phase III Pediatric Clinical Trials

Trial No. [Report No.]	Country No. of Sites [Start Date-End Date]	Contrast Agent-mgI/mL (Lot No.)	N/n [a] (M/F)	Age (yr) Mean (Range)	Total Injection, Mean (Range) Volume (mL) Mean (Range)	Total Injection, Mean (Range) Dose (gI) Mean (Range)	SNDA Location (Vol:Pg) Full Report, Data Listings	SNDA Location (Vol:Pg) Case Report Forms
Phase III Excretory Urography Controlled, Double-Blind, Randomized, Parallel-Group Trial (Nonionic Contrast Agent Comparator)								
DXV037 [2510]	France 3 [May 1994-February 1995]	VIS-270 (312001) VIS-320 (309108) OMN-300 (311106)	25/22 (13/9) 25/25 (15/10) 25/25 (14/11)	4.13 yr 3.76 yr 4.94 yr	23.6 24.4 27.7	6.37 7.82 8.32	16:152-419 17:1-96	17:46-70
DXV041 [2513]	Sweden 1 [March 1994-February 1995]	VIS-270 (312000) VIS-320 (309107) OMN-300 (311107)	26/26 [c] (10/16) 27/27 [c] (13/14) 25/25 (11/14)	3.83 yr 4.87 yr 3.70 yr	30.5 32.5 30.1	8.23 10.41 9.04	17:105-385 18:1-97	18:47-67

[a] N=number of patients enrolled/randomized; n=number of patients evaluable for safety. Numbers for males (M) and females (F) include only those evaluable for safety.

[b] Minimum age listed is at time of examination.

[c] Includes three 'pilot' patients (one in the VIS-270 group and two in the VIS-320 group) who were enrolled in an open Phase II portion of the trial and who were evaluable for safety.

REF: Trial Reports 2510 (Trial DXV037) and 2513 (Trial DXV041)

Table 7.1.2A
Angiocardiography: Summary of Demographic Information for Each Trial, and for All Three Trials Combined, by Group

Demographic Parameter	39998-013		39998-018	DXV036		Combined	
	VIS-320 (N=58)	OMN-350 (N=59)	VIS-320 (N=41)	VIS-320 (N=62) [a]	OMN-350 (N=26)	VIS-320 (N=161) [a]	OMN-350 (N=85)
Age (yr)							
Mean (SD)	2.14 (2.65)	1.99 (2.71)	1.70 (2.42)	3.19 (3.17)	4.63 (4.19)	2.43 (2.86)	2.80 (3.44)
Range							
Weight (kg)							
Mean (SD)	10.26 (8.14)	9.71 (9.04)	9.12 (6.63)	13.16 (8.70)	18.42 (14.41)	11.08 (8.15)	12.37 (11.60)
Range	2.3-39.0	2.1-46.0	2.5-37.0		3.8-54.5		
Height (cm)							
Mean (SD)	77.1 (25.8)	74.3 (26.1)	74.4 (22.4)	N=61 88.5 (26.1)	100.0 (31.8)	N=160 80.8 (25.7)	82.2 (30.2)
Range							
Body Surface Area (m^2)							
Mean (SD)	0.448 (0.260)	0.424 (0.263)	0.417 (0.218)	N=61 0.555 (0.270)	0.694 (0.382)	N=160 0.481 (0.259)	0.507 (0.327)
Range							
Sex, N (%)							
Male	30 (52)	30 (51)	27 (66)	30 (48)	15 (58)	87 (54)	45 (53)
Female	28 (48)	29 (49)	14 (34)	32 (52)	11 (42)	74 (46)	40 (47)
Race, N (%)							
Caucasian	44 (76)	44 (75)	25 (61)	60 (97)	26 (100)	129 (80)	70 (82)
Black	6 (10)	6 (10)	14 (34)	2 (3)	0	22 (14)	6 (7)
Oriental	0	2 (3)	1 (2)	0	0	1 (1)	2 (2)
Other	8 (14)	7 (12)	1 (2)	0	0	9 (6)	7 (8)

[a] N=total number of patients in the respective group unless otherwise noted for a particular demographic parameter.
SD=standard deviation.
REF: Appendices 3.1.1 and 3.1.2

Table 7.1.6.1
Angiocardiography: Summary of Dosing and Injection Information for Each Trial, and for All Three Trials Combined, by Group

Dosing Parameter	39998-013		39998-018	DXV036		Combined	
	VIS-320 (N=58) [a]	OMN-350 (N=59) [a]	VIS-320 (N=41)	VIS-320 (N=62) [a]	OMN-350 (N=26)	VIS-320 (N=161) [a]	OMN-350 (N=85) [a]
Number of Injections Mean (SD) Range	3.3 (1.4)	3.0 (1.3)	2.8 (1.5)	2.7 (1.3)	2.9 (0.9)	2.9 (1.4)	3.0 (1.2)
Total Dose (gI) Mean (SD) Range	15.95 (14.48)	14.80 (11.37)	11.86 (6.74)	16.25 (9.67)	21.47 (12.67)	15.02 (11.19)	16.84 (12.11)
Total Dose (gI/kg) Mean (SD) Range	1.68 (0.85)	1.80 (1.06)	1.53 (0.74)	1.37 (0.56)	1.39 (0.48)	1.52 (0.73)	1.68 (0.94)
Total Volume (mL) Mean (SD) Range	49.8 (45.3)	42.3 (32.5)	37.1 (21.1)	50.8 (30.2)	61.3 (36.2)	46.9 (35.0)	48.1 (34.6)
Total Volume (mL/kg) Mean (SD) Range	5.25 (2.66)	5.15 (3.04)	4.80 (2.32)	4.27 (1.74)	3.98 (1.38)	4.76 (2.28)	4.79 (2.69)
Injection Rate (mL/sec) Mean (SD) Range	N=52 12.72 (5.86)	N=55 12.51 (5.90)	11.44 (5.19)	N=60 11.23 (5.20)	13.77 (6.75)	N=153 11.80 (5.44)	N=81 12.91 (6.17)

[a] N=total number of patients in the respective group unless otherwise noted for a particular dosing parameter.
SD=standard deviation.
REF: Appendices 3.5.1.1 and 3.5.1.2

Table 8.1.2A
Intravenous (CT Head, CT Body and Urography): Summary of Demographic Information for All Trials Combined, by Group

Demographic Parameter	VIS-270 (N=144) [a]	VIS-320 (N=154) [a]	ALL VIS (N=298) [a]	OMN-300 (N=150) [a]
Age (yr) Mean (SD) Range	5.38 (4.26)	5.45 (3.95)	5.42 (4.10)	5.56 (4.30)
Weight (kg) Mean (SD) Range	21.18 (13.40)	21.21 (13.16)	21.20 (13.25)	21.63 (13.58)
Height (cm) Mean (SD) Range	N=138 106.8 (30.0)	N=148 107.6 (30.5)	N=286 107.2 (30.2)	N=149 109.2 (30.2)
Body Surface Area (m^2) Mean (SD) Range	N=138 0.776 (0.354)	N=148 0.780 (0.357)	N=286 0.778 (0.355)	N=149 0.795 (0.358)
Sex, N (%) Male Female	78 (54) 66 (46)	87 (56) 67 (44)	165 (55) 133 (45)	81 (54) 69 (46)
Race, N (%) Caucasian Black Oriental Other	120 (83) 18 (13) 2 (1) 4 (3)	122 (79) 22 (14) 4 (3) 6 (4)	242 (81) 40 (13) 6 (2) 10 (3)	122 (81) 20 (13) 2 (1) 6 (4)

[a] N=total number of patients in the respective group unless otherwise noted for a particular demographic parameter.
SD=standard deviation.
REF: Appendix 4.1.1

Table 8.1.6
Intravenous (CT Head, CT Body and Urography): Summary of Dosing and Injection Information for All Trials Combined, by Group

Dosing Parameter	VIS-270 (N=144)	VIS-320 (N=154)	ALL VIS (N=298)	OMN-300 (N=150)
Total Dose (gI) Mean (SD) Range	11.80 (8.83)	14.06 (10.03)	12.97 (9.52)	13.42 (9.38)
Total Dose (gI/kg) Mean (SD) Range	0.55 (0.14)	0.67 (0.20)	0.61 (0.18)	0.62 (0.16)
Total Volume (mL) Mean (SD) Range	43.7 (32.7)	43.9 (31.4)	43.8 (32.0)	44.7 (31.3)
Total Volume (mL/kg) Mean (SD) Range	2.05 (0.53)	2.10 (0.63)	2.08 (0.58)	2.08 (0.54)
Injection Rate (mL/sec) Mean (SD) Range	0.46 (0.31)	0.41 (0.26)	0.44 (0.29)	0.50 (0.37)

SD=standard deviation.
REF: Appendix 4.5.1

PHASE - 1 PHARMACOKINETICS

Protocol #39998-018
Study Report #2493

Investigators - The names and study sites of the investigators and the number of patients enrolled and dosed at each following site:

List of Investigators and Patient Enrollment

Center	Name & Affiliation	Enrolled/Dosed
002	Thomas R. Lioyd, M. D. C.S.M. Childrend's Hospital Ann Arbor, MI	8/8
003	Benjamin Victorica, M. D. University of Florida Hosp. Gainesville, FL	8/8
004	R. Leff / R.Ardinger, Jr.,M, D. Kansas Medical Ctr. Kansas City, KS	3/3
005	Vincent R. Zales, M. D. The Deborah H & L Center Browns Mills, NJ	7/7
006	Michael L. Epstein, M. D. Children's Hospital of Michigan Detroit, MI	5/5
007	Walter H. Johnson, Jr., M. D. Univer. Hospital of Alabama Brimingham, AL	10/10
008	Thomas L. Slovis, M. D. Children's Hospital of Michigan Detroit, MI	2/2
7 Centers		43/43

Study Objectives - To determine the pharmacokinetic profile of VIS-320 mgI/mL in plasma in pediatric patients undergoing intravascular, administration. To assess the safety of VIS-320 in pediatric patients undergoing intravascular administrations by evaluating adverse events, injection-associated discomfort and/or distress, vital signs, and clinical laboratory parameters and, in cardioangiography patients only, hemodynamics and ECGs.

Study Design - This was a Phase-1, open-label multicenter, pharmacokinetic study assessing the pharmacokinetics and safety of VISIPAQUE in pediatric patient. A total of 43 pediatric patients was enrolled and/or dosed at 7 centers, with from 2-10 patients per center. The data from 40 pediatric patients were used in the pharmacokinetic analyses. Two patients (#003-0008 and 006-0005) that had incomplete pharmacokinetic sampling data excluded from all summaries and data analyses, were replaced in this trial. Patients were enrolled into one of five age groups; (newborn to <2 months, 2 to <6 months, 6 to <12 months, one to <3 years, & 3 to <12 years).

Demographic and Dosage Information:

A total of 43 patients (27 males and 16 females) was conducted in 7 study centers. The majority of the patients were male Caucasian. The mean age of the patients was 1.87 years, the mean weight was 9.7 kg, and the mean height was 75.8 cm (see Table below):

Summary of Demographic Characteristics by Age Group

Demographics No. of Patient	<2 mo (N=8)	2 - <6 mo (N=9)	6 - <12 mo (N=10)	1 - <3 yr (N=8)	3 - <12 yr (N=8)	All Age Group (N=43)
Gender, N (M/F)	(4/4)	(5/4)	(7/3)	(5/3)	(6/2)	(27/16)
Age (yr)						
Mean	0.06	0.31	0.69	1.90	6.88	1.87
Range						
Weight (kg)						
Mean	3.7	4.9	7.6	10.7	22.9	9.7
Range						
Height (cm)						
Mean	52.0	59.1	70.5	81.9	119.0	75.8
Range						
Race, N (Cau/B/O/Other)	(6/2/0/0)	(6/3/0/0)	(4/5/0/1)	(4/3/1/0)	(6/2/0/0)	(26/15/1/1)

The dose injection information was divided into five age groups. Overall, the mean dose of VIS-320 mgI/mL was 1.49 gI/kg for 43 patients. The mean total volume of VIS-320 was 4.67 mL/kg. Detail of the dose distribution is presented in Table below:

Drug Administration Informationby By Age Group

Dosage (mo/yr) No. of Patient	<2 mo (N=8)	2 - <6 mo (N=9)	6 - <12 mo (N=10)	1 - <3 yr (N=8)	3 - <12 yr (N=8)	All Age Group (N=43)
Dose (gI)						
Mean	6.14	8.62	11.14	16.63	17.92	11.97
Range						
Dose (gI/kg)						
Mean	1.73	1.73	1.50	1.67	0.81	1.49
Range						
Total Volume (mL)						
Mean	19.20	26.94	34.80	51.96	56.00	37.39
Range						
Total Volume (mL/kg)						
Mean	5.41	5.40	4.68	5.22	2.53	4.67
Range						

Risk Factors - The majority of patients had more than one referring diagnosis. The most common referring diagnoses were ventricular septal defect, patent ductus arteriosus, aortic stenosis, tetralogy of Fallot, ASD, VSD and aortic hypoplasia (ref. Vol. 6. Appendix 2.3.4. p216-7). The most frequently reported risk factor was congestive heart failure, asthma, & hypertension (ref. Vol. 6. Appendix 2.3.6. p220).

Medications - The majority of patients (84%) in this study received one or more concurrent medications (the most common primary medications were cardiovascular, central nervous system, and others).

Efficacy Results - Evaluation of efficacy data was not a primary endpoint for this study; however, the quality of enhancement or visualization for the radiographic procedure was rated by the investigator using a 4-point scale. The quality of visualization was graded as adequate for diagnosis in all 43 patients stated by the sponsor.

Safety Results - Blood samples were obtained from each patient for pharmacokinetic analyses. Safety was assessed by monitoring vital signs, hemodynamics ECGs, clinical laboratory parameters and adverse events.

Vital signs - Supine systolic/diastolic blood pressure and pulse rate were measured prior to and immediately after the procedure, and one day (16-32 hours) after injection. There were no clinically significant postinjection changes from baseline values. Although some individual variation was noticed. The scatter plots did not reveal any systematic shifts or trends.

Hemodynamics - Two patients (#008-0001, #008-0002) who underwent CT procedures by intravenous route. All other patients underwent cardioangiography and showed no clinically relevant changes.

Electrocardiography (ECG) - None of the 41 patients experienced changes from baseline value in ECG parameters. Only one patient (#005-0003) experienced premature atrial contractions (PAC) with mild intensity which lasted approximately 4 hours in duration.

Laboratory Parameters - Statistically significant mean changes from baseline values were observed for these parameters including increases in sodium chloride, and neutrophils, decreases in hematocrit, hemoglobin, lymphocytes, RBC and platelet count. The majority of changes were no more than 40% of the reference range. Four patients had increases in serum creatinine values greater than 40% of the reference range post-procedural.

Pharmacokinetic Profile - (details see biopharm review)

Data shown that mean k_{el} of VIS-320 was statistically significantly lower in newborn to <2-month-old compared with older children <12 years of age. Thus, with increasing postnatal age and a concurrent increase in renal maturity, iodixanol is excreted more rapidly (see Table below):

Terminal Elimination Rate Constant (k_{el})
and Half-Life ($t_{1/2}$) by Age Group

		$k_{el}(hr^{-1})$		$t_{1/2}(hr)$	
Age Group	(N)	Mean	(SD)	Mean	(SD)
Newborn to <2 months	8	0.185	0.006	4.14	1.41
2 to <6 months	8	0.256	0.046	2.79	0.55
6 months tpo <1 year	9	0.299	0.042	2.36	0.37
1 to <3 years	7	0.322	0.058	2.23	0.51
3 to <12 years	8	0.307	0.071	2.36	0.52

In newborn infants <2 months of age, the half-life of iodixanol was estimated approximately 4.1 hours. Children under 12 years of age, the half-life of iodixanol was estimated 2.3 hours (approximately that of adults with normal renal function 2.1 hours). Since the renal elimination rate is directly proportional to GRF and because, in adults, Visipaque is excreted unchanged in the urine, it is expected that, the renal elimination rate in children will follow a similar trend to that of adult glomerular filtration rate (GRF). The GRF for children, as compared to that of adults, increases with age as shown in Table below:

Normal GRF (mL/min/1.73m^2) Values, by Age

		Months				Years			
Age	Newborn	2	6	8	12-19	3	9	12	Adult
GRF	38.5	70.2	110.7	110	117.5	127	127	127	127
Adult GRF (%)	30	55	87	87	93	100	100	100	100

Adverse events:

Deaths - Patient (#002-0005), a 27 month-old female with hypoplastic left heart syndrome. On May 23, 1995, she underwent cardioangiography for persistent pleural effusion and received 41 mL of VIS-320 mgI/mL. Serum creatinine was at completion of the catheterization. On May 25, patient developed acute renal failure with severe intensity. Her serum creatinine rose to on 25th and peak value at on 28th of May. The patient was treated initially with fluids, potassium restriction and she ultimately required peritoneal dialysis. The patient did poorly and expired on June 17th.

Two serious adverse events were reported after the procedure. Patient (#002-0004) experienced cardiac arrest 5 days after completing the trial and the other patient (#002-0006) experienced left lung atelectasis and collapsed about 4 days after the study. These events were included in all adverse event listings.

Adverse events other than injection-associated discomfort:

Eighteen (18) of 43 (42%) patients who experienced 27 adverse events and occurrences for this site. The most frequently occurring adverse events were nausea (7%) & vomiting (12%) and arrhythmias (7%) with mild to severe intensity. Most commonly reported adverse events listed in Table below:

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By Age Group

Adverse Event No. of Patient No. of pts /c AEs	<2 mo (N=8) 4	2 - <6 mo (N=9) 3	6 - <12 mo (N=10) 4	1 - <3 yr (N=8) 5	3 - <12 yr (N=8) 2	Combined (N=43) 18(42%)
Vomiting		1	1	2	1	5(12%)
Anemia	2		1	1		4 (9%)
Nausea				1	2	3
Arrhythmia	1			1	1	3
Hypokalemia	2					2
Renal failure				1		1
Hyponatremia	1					1
Apnea		1				1
Hypoxia	1					1
Fever			1			1
Convulsion	1					1
Rash	1					1
Leukocytosis				1		1
L. Lung Collapse					1	1
Cardiac arrest		1				1
	9	3	3	7	5	27

Reviewer's Comment:

One death and two serious adverse events have been reported in this phase-1 trial and appears to be related to the study drug.

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U. S. CONTROLLED CLINICAL TRIALS
(PEDIATRIC CARDIOANGIOGRAPHY)
PIVOTAL 1

Study Report #1968
Protocol No. 39998-013

List of Investigators and Patient Enrollment

Center	Name & Affiliation	Enrolled/Dosed
001	Donald Girod, M. D. James Whitcomb Hospital for Children Indianapolis, IN	33/33
002	James Wiggins, M. D. Children's Hospital Denver, CO	22/22
003	Vincent Zales, M. D. Children's Memorial Hospital Chicago, Ill	30/29
004	Benjamin Victorica, M. D. University of Florida Hosp. Gainesville, FL	6/6
005	Paul Julsrud, M. D./ Donald Hagler, M. D. Mayo Clinic Rochester, MN	12/12
031	Michael Vance, M. D. Geisinger Medical Ctr. Danville, PA	8/8
032	Jonathan Rome, M. D. Children's Hospital Philadelphia, PA	7/7
7 Centers		118/117

*One patient did not receive clinical trial because of lack of venous access.

Study Objectives:

To compare the efficacy of iodixanol-320 mgI/mL vs iohexol-350 mgI/mL in pediatric patients requiring angiocardiography by evaluating the overall quality of radiographic visualization provided by the contrast agent, obtaining a radiographic diagnosis and assessing the diagnostic utility of the contrast medium.

To compare the safety of iodixonal-320 mgI/mL vs iohexol-350 mgI/mL in pediatric patients requiring angiocardiography by measuring vital signs, hemodynamic parameters, ECGs, laboratory parameters, adverse events and injection-associated discomfort.

Study Design:

This was a Phase-3, multicenter randomized, double-blind, parallel clinical trial. The initial protocol, which included pediatric patients >28 days to <18 years of age, was amended to include patients from birth (>36 weeks gestation and >2000 g of body weight) to <12 years of age.

Demography:

A total of 118 pediatric patients (61 males, 57 females) from seven (7) study sites were enrolled in the trial with between 3 - 17 patients assigned to each contrast agent group at each center. Across the two contrast groups , the ages of patients ranging from one day to 10.6 years. Seventeen (17) patients in each contrast agent group were neonates (<28 days). The race and gender distribution and means for age, weight and height were listed below:

Summary of Demographic Characteristics, by Group

Demographic Characteristics		VIS - 320mgI/mL (N - 58)	OMN - 350mgI/mL (N - 60)
Gender(m/f)		30 / 28	31/ 29
Age (yr)	Mean(SD)	2.14 (2.65)	2.07 (2.76)
	Range		
Weight(kg)	Mean	10.26 (8.14)	9.91 (9.10)
	Range		
Height(cm)	Mean	77.11 (25.80)	75.04 (26.49)
	Range		
Race(Cau/B/Or/Others)		(44/6/0/8)	(44/7/2/7)

Reviewer's Comment - Demographic data on patients within two group at the one study center were similar in gender, age and weight except the race were unevenly distributed. When gender and race were stratified by age group (0 to <28 days, 29 days to <3 years and 3 years to <12 years), however, the distribution of race was generally similar within each drug group and between groups, while the distribution of gender varied slightly among the age groups both within and between drug groups.

History of Sensitivity - Seventeen (17) of 118 patients (14%) had a history of sensitivity to medication and/or allergens (10 of the 58 patients in the VIS-320 group and 7 of the 60 patients in the OMN-350 group. Allergen sensitivities included eggs, milk products, and skin contact with electrodes. Medication sensitivities; primarily antibiotics.

High-Risk Patients (ref.Table 8.3.2. p54) - The potential risk factors identified for 45 of the 118 patients (38%); includes 19 of 58 patients in the VIS-320 group and 26 of the 60 patients in the OMN-350 group. The most frequently reported risk factor was congestive heart failure, which was identified for 38 patients (17 VIS-320 group and 21 OMN-350 group). Five patients had hypertension (2 VIS-320 group and 3 OMN-350 group), and three patients had asthma (2 VIS-320 group and 1 OMN-350 group).

Concurrent Medications - A total of 118 patients enrolled in this pivotal trial, 103 patients received one or more concurrent medications during the period from 24-hour prior to the procedure and one day post-cardioangiography.

These included 50 of the 58 patients in the VIS-320 group and 53 of the 60 patients in the OMN-350 group (as presented in Tables 8.4.1, & 8.4.2). The most frequently received primary medications were cardiovascular system, alimentary tract, metabolism and CNS medications. The most frequently received secondary medications were cardiac therapy drugs (47% of VIS-320 group and 40% of OMN-350 group), diuretics (47% of VIS-320 group and 40% of OMN-350 group), and systemic antibiotics (31% of VIS-320 group and 42% of OMN-350 group).

Reviewer's Comment - The two groups were generally similar with respect to usage of concurrent medications.

Dosage and Injection Information - The overall distribution of the mean total dose (in gI and gI/kg), volume (in mL and mL/kg) and injection duration were generally similar between the drug groups. When dosing data were stratified by age group, the mean total doses and mean total volumes within each group were similar for the three age groups (see Table below).

Summary of Dosing Information by Group
(stratified by age groups)

	VIS - 320				OMN - 300			
Age groups No. of Pts	0 -<28dy (N=17)	29dy-<3yr (N=24)	3-<12 yr (N=17)	Total (N=68)	0-<28dy (N=17)	29dy-<3yr (N=27)	3-<12yr (N=15)	Total (N=59)
Dose (gI)								
Mean	**5.06**	**14.93**	**28.27**	**15.95**	**5.43**	**13.82**	**27.16**	**14.80**
Range								
Dose (gI/kg)								
Mean	**1.62**	**1.88**	**1.46**	**1.68**	**1.75**	**2.03**	**1.46**	**1.80**
Range								
Volume (mL)								
Mean	**15.82**	**46.65**	**88.35**	**49.83**	**15.52**	**39.49**	**77.60**	**42.27**
Range								
Volume (mL/kg)								
Mean	**5.06**	**5.88**	**4.56**	**5.25**	**4.99**	**5.79**	**4.17**	**5.15**
Range								

Dose information by injection site - These injection sites included the left ventricle (73%), right ventricle (48%), aortic root (32%), aortic arch (21%), and pulmonary artery (20%); all other injection sites for <10% of the patients.

Reviewer's Comment - No disagreement with the sponsor's analysis.

Protocol Variation/Patient withdrawal - There were no variation or withdrawn in this clinical trial. One patient (#003-0361) in the OMN-350 group was withdrawn from the trial prior to receiving contrast agent therefore, this was excluded from all dosing, efficacy and safety analyses.

Efficacy Results - The overall quality of radiographic visualization was graded as good/excellent (100%) in the VIS-320 group versus 98% of the patients in the OMN-350 group. Only one patient in OMN-350 group had non-diagnostic value because of technical difficulty. For the majority of patients in both groups, the contrast agent increased the diagnostic confidence in 84% (49/58) in the VIS-320 group and 81% (48/59) in the OMN-350 group (ref. Table 9.2B. P70).

Summary of the Contribution of the Contrast Agent to the Ability to Make a Radiographic Diagnosis

Contribution of Contrast Agent	VIS-320 (N=58)	OMN-350 (N=59)
Increased confidence in diagnosis	49(48%)	48(81%)
Increased definition of heart chamber(s)	45(78%)	44(75%)
Increased definition of vascular structure(s)	45(78%)	47(80%)
Provided add. Detailed anato. Information	29(50%)	30(51%)
Other	1 (2%)	2 (3%)

The radiographic results in the VIS-320 group comfirmed the referring diagnosis or presenting symptoms in all 58 patients versus 57 of the 59 (97%) in the OMN-350 group. The sponsor was blinded to the response for the relationship between the radiographic diagnosis and the primary referring diagnosis and/or presenting symptoms (see ref. Table 9.2C or p71).

Additional Information - One hundred sixteen (116) of the 117 patients had additional diagnostic information obtained prior to or 3 days after the study procedure (58 patients in each group). One patient in each group (003-0355 VIS-320 and 003-0301 OMN-350) had prior additional diagnostic information obtained from a source that was not consistant with the radiographic diagnosis (see Table below).

Summary of Additional Diagnostic Information

Sources of additional diagnostic information	VIS-320	OMN-350
Number of patients	58	58
Biopsy	4/4	2/2
Surgery	26/26	27/27
Echocardiography	53/54	55/56
Additional imaging	13/13	14/14
Other	2/2	0

Reviewer's Comment - No disagreement with the sponsor's analysis.

Safety Results:

Vital Signs - Pulse rate and both systolic/diastolic blood pressures were recorded immediately prior to and at 30, 60 minutes and 24 hours after the contrast administration. Although some individual variation was noticed, there were no clinically significant trends in change from baseline value in any of the vital signs parameters following the administration contrast media at 30, 60 minutes and 24-hour time points. Scatterplots of post-injection vital signs versus baseline values did not reveal any systemic shifts.

Hemodynamics - Both heart rate and intravascular blood pressures were also recorded prior to and at 30, 60, and 120 seconds after the contrast administration. Although some individual variation was noticed, none of the changes in hemodynamic measurements was considered to be a clinically relevant change from baseline value. Only 5 patients (2 VIS-320 group and 3 OMN-350 group) had a clinically relevant change in hemodynamic measurements (ref. Table 10.3. Vol. 9. p86).

Electrocardiogram Parameters - Numeric changes from baseline, percent changes for PR and RR intervals in (msec) and QT, (corrected QT interval) and mean changes from baseline for ST segment and T wave amplitude in (mV) for each injection site.

There were 9 patients (6 VIS-320 group and 3 OMN-350 group) who experienced at least one post-injection arrhythmia. Six of the VIS-320 patients experienced a total of 13 episodes of arrhythmia and 3 of the OMN-350 patients experienced a total of 8 episodes of arrhythmia (see ref. Table 10.5, p89).

Reviewer's Comment - There were no clinically significant differences observed in either individual percent changes from baseline in PR, R-R intervals, QTc, or in the mean changes from baseline in ST segment, and T-wave amplitude among injection sites within each contrast group or between groups. Four patients (#002-0209, #003-0355 VIS-320 group, and #003-0353, #003-0358 OMN-350 group) had post-injection changes in ECG measurements.

Laboratory Results:

The laboratory parameters showed that there were no statistically significant differences between contrast agents in 40% of the reference range, however, there was greater changes of 80% of the reference range in comparison with VIS-320 group versus OMN-350 group. The distribution of patients with changes in hematology, blood chemistry and urinalysis parameters greater than 80% of the reference range are presented in Table below:

Laboratory Parameters	VIS-320 No.	Decrease	Increase	OMN-350 No.	Decrease	Increase
Hematocrit	34	2 (6%)	0	33	2 (6%)	0
Lymphocytes	36	4 (11%)	0	34	2 (6%)	0
Neutrophils	36	0	4 (11%)	34	0	3 (9%)
WBC	36	0	3 (8%)	34	0	4 (34%)
AST(SGOT)	37	0	7 (19%)	36	0	14 (14%)
S. Creatinine	37	0	3 (8%)		0	0
Glucose				33	13 (39%)	2 (6%)
Total Protein				36	0	2 (6%)
Specific gravity				9	2 (22%)	0

Reviewer's Comment - No disagreement with the sponsor's analysis. Evaluation of the scatterplots of pre- & post-injection values for laboratory parameters indicated some relatively large and sporadic individual value changes from baseline. No good explanation given by the sponsor. Two patients in the VIS-320 group (#002-0253, #003-0304) had post-injection value increases in serum creatinine that were greater than 80% of the reference range. These patients recovered. Volume 9. p92 and Vol. 10. p116. Appendix 4.3.1. recorded that 3 of 37 patients had post-injection increases in serum creatinine which were greater than 80% of the reference range, but one patient still can not be accounted for. There were no value increases of serum creatinine in the OMN-350 group, however.

Injection-Associated Discomfort - There were 8 of the 117 (7%) patients experienced injection-associated discomfort (2 patients in the VIS-320 group and 6 in the OMN-350 group). The injection-associated discomfort were mild in intensity and lasted from 5 seconds to two minutes duration.

Group No. Patient	Experienced Discomfort	Intensity Mild	Moderate	Severe	MAX Duration (mm:ss)
VIS-320 (N=58)	2(3.4%)	1	0	1	2:00
OMN-350(N=59)	6(10.2%)	5	1	0	1:00
	8	6	1	1	2:00

Adverse events other than injection-associated discomfort - Sixteen of the 117 patients (14%) who experienced a total of 24 adverse events during the study period (4 deaths were excluded). Adverse events information is summarized in Table below:

Summary of Adverse Events by Group & Intensity

No. Pts with ADR	VIS - 320 (N = 58)				OMN - 350 (N = 59)			
Adverse Events	Mild	Mod.	Severe	Total	Mild	Mod.	Severe	Total
Fever	0	2	1	3	0	0	1	1
Nausea	1	0	0	1	0	0	0	0
Vomiting	1	1	0	2	0	1	1	2
Arrhythmia	2	0	0	2	2	0	2	4
Rash	1	0	1	2	0	0	0	0
Acute Renal Failure	0	1	0	1	0	0	1	1
Cardiogenic Shock	0	0	1	1	0	0	1	1
Flushing	1	0	0	1	0	0	1	1
DIC	0	0	0	0	0	0	1	1
	6	4	3	13	2	1	8	11

Reviewer's Comment - The sponsor provided adverse events list which was inadequate. Arrhythmia, flushing and cardiogenic shock should also be included in the list. Ten (10) of 58 patients received VIS-320 and 6 of 59 patients received OMN-350 who experienced a total 13 and 11 adverse events, respectively. The most frequently occurring adverse events were fever, nausea & vomiting, arrhythmia, rash and acute renal failure. There were no statistical differences between the two groups.

Deaths - Four deaths (3 patients in the VIS-320 group and one patient in the OMN-350 group) have been reported in this clinical trial (see Table below):

Group Patient ID	Age Sex	Weight (kg)	Dose (mL)	Onset	Duration	Intensity	Adverse Event	Relationship To C. Agent
VIS-320								
001-0181	19d/m	2.3	9	14days	13days	severe	sepsis	no
001-0184	08d/f	2.5	10	4days	1day	severe	sepsis & MI	no
002-0209	12m/f	8.5	42	2days	10hrs	severe	cardiogenic shock	uncertain
OMN-350								
002-0210	12m/m	8.5	33	60hrs	2hrs	severe	cardiogenic shock DIC,Acute RF	uncertain

Serious Adverse Events - Five of the 58 patients (8.6%) in the VIS-320 group had a total of 6 serious adverse events and none in the OMN-350 group. These events are presented in the Table below:

Group Patient I D	Age Sex	Weight (kg)	Dose (mL)	Onset	Duration	Intensity	Adverse Event	Relationship To C. Agent
VIS-320								
001-0186	10d/f	3.5	25	30min	8min	mild	arrhythmia	no
001-0189	10d/m	2.9	23	21hrs	11hrs	severe	enterocolitis	no
003-0302	05m/f	4.0	41	3days	unkn.	mod	pneumonia	no
003-0304	27m/f	10.0	91	11hrs	6days	severe	rash, fever & acute RF	unceretain
003-0383	18d/f	3.0	21	22hrs	8hrs	mod	fever	unknown

Reviewer's Comment - No disagreement with the sponsor's analysis.

Reviewer's Evaluation and Summary:

The study report #1968 consists of one protocol (39998-013) with 7 different clinical trials conducted under this protocol which supported the safety and efficacy of the drug. A total of 117 patients (58 patients in the VIS-320 group and 60 patients in the OMN-350 group) were studied. VIS-320 was given to 58 patients (30 males and 28 females), aged (mean 2.14) and weighing (mean 10.26). OMN-350 was given to 60 patients (31 males and 29 females), aged (mean 2.07) and weighing (mean 9.91). Dosing information based upon injection site. The distribution of age, gender, weight, and injection information were generally similar between the two contrast agent groups with no statistically significant differences observed for the analyses of demographic parameters. Race, however, was unevenly distributed. One OMN-250 patient withdrew from the clinical trial before dosing.

Efficacy - The overall assessments of visualization for both groups of the study were diagnostic (good/excellent). No clinically significant differences were observed between the two treatment groups.

Safety - There were no statistically significant differences between the two drug groups relative to the vital signs, ECGs, blood, and urine parameters. Although transient individual patient changes in blood chemistry occurred in both drug groups, none of these changes were serious or caused any medical concern. With regard to hemodynamics; no trends were observed in the distribution of changes from baseline in hemodynamic measurements across the injection sites within a contrast agent group or between groups. With respect to the drug tolerance, 4 deaths (3 patients in the VIS-320 group and one in the OMN-350 group) and 5 serious adverse events (4 in the VIS-320 group, one in the OMN-350 group) have been reported. The most frequent adverse events being mild, and moderate-severe nausea, vomiting, fever, and arrhythmia.

Reviewer's Comment - This reviewer believes that the study data supports the safety and effectiveness claim that the VIS-320 mgI/mL is comparable to OMN-350 mgI/mL for pediatric cardioangiography.

EUROPEAN CLINICAL CONTROLLED TRIAL
Study Report (#2509) (PEDIATRIC CARDIOANGIOGRAPHY)
Protocol #DXV036 PIVOTAL 2

Principal Investigators:

Center 1	Center 2
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Objectives:

The objective of this phase-2 (open) clinical study was to generate preliminary safety data for use of VIS-320 in pediatrics.

The objectives of this phase-3 study was to evaluate the drug tolerance and diagnostic efficacy of the investigational contrast agent VIS-320 mgI/mL

To compare the safety of VIS-320 versus OMN-350 in pediatric patients requiring angiocardiography by measuring vital signs, hemodynamic parameters, ECGs laboratory parameters, adverse events and injection-associated discomfort..

Study Design:

This was a combined phase II/III clinical trial in pediatric patients referred for cardioangiography. This study consisted of an open phase-II which VIS-320 mgI/mL was given for 10 patients, and a phase-III, randomized, double-blind, parallel, two-group study for 78 patients conducted at two centers. A total of 88 pediatric patients (10 patients with an open phase-2 and 78 patients in the phase-3) successfully completed the study. None was excluded prior to the administration of the contrast agent.

Demographics:

Phase-2 study - Eight of the 10 pediatric patients were Caucasians and 2 were black. Sex were equal. Their age varied between
Their weight between (see Table below).

An Open Phase-2, Patient Demographic Characteristics

Demographic Characteristics		VIS - 320 mgI/mL <2 yrs(7)	>2 yrs(3)	Total(10)
Gender(M/F)		5/2	0/3	5/5
Age(mons)	Mean	11.9	45.7	22.0
	Min/Max			
Weight(kg)	Mean	8.2	16.9	10.8
	Min/Max			
Height(cm)	Mean	71.7	100.0	80.2
	Min/Max			
Race	(Cau/B)	5/2	3/0	8/2

Phase-3 study - A total of 78 pediastric patients were enrolled at 2 study centers. VIS-320 was given to 52 patients (25 males and 27 females), aged (mean 41.3) and weighing (mean 13.6). OMN-350 was given 26 patients (15 males and 11 females), aged (mean 55.6) and weighing (mean 18.4).

COMBINED CENTER 1 AND CENTER 2

Demographic Characteristics		Total 78	VIS - 320 mgI/mL <2 yrs (26)	>2 yrs (26)	Total (52)	OMN-350 mgI/mL <2 yrs (8)	>2 yrs (18)	Total (26)
Gender(M/F)		40/38	11/15	14/12	25/27	5/3	10/8	15/11
Age(mons)	Mean	46.1	9.9	72.8	41.3	6.6	77.3	55.6
	Min/Max							
Weight(kg)	Mean	15.2	6.9	20.3	13.6	6.4	23.8	18.4
	Min/Max							
Height(cm)	Mean	93.3	66.8	112.5	90.1	64.1	115.9	100.00
	Min/Max							
Race	Caucasian	78	26	26	52	8	18	26

Reviewer's Comment - There were no statistically significant differences in gender, age, weight or height between the two contrast agent groups. Race however, was unevenly distributed.

Clinical diagnosis - The most common cardiac abnormalities are tabulated as follows:

	Phase II VIS-320(N=10)	Phase III VIS-320(N=52)	OMN-350(N=26)
Ventricular septal defect	2 (20%)	14 (27%)	7 (27%)
Atrial septal defect	3 (30%)	5 (10%)	3 (21%)
Tetralogy of Fallor	0	6 (12%)	4 (15%)
Single ventricle	1	6	2 (8%)
Valvular incompetence	0	3	5 (19%)

Both cyanosis and symptoms of congestive heart failure were seen more often in the VIS-320 group (38% & 25%, respectively) than in the OMN-350 group (19% & 12%, respectively). The other clinical symptoms were fatigue, heart murmurs and failure to thrive (ref. Tables 2b.2-4. Vol. 13. p103).

History of high-risk patients - None of the 10 patients had any risk factors relevant to the use of radiocontrast agents noted in the Pilot study. In the phase-3 study, however, there were four patients had allergies (3 in the VIS. group one in the OMN group, respectively). In addition, there were two patients had asthma in the VIS. Group. In the phase-3 clinical trial, there were 23 patients who received VIS. and 12 patients received OMN. had 33 and 20 previous studies with a iodinated contrast agent, respectively.

Medications:

Phase-2 - All the patients received pre-medication (sedation only; ketamine and midazolam as described in the protocol) and medication during the examination (sedation for all patients and heparin for 2 patients).

Phase-3 - Forty-seven (47) patients (32 VIS group, & 15 OMN group), received concomitant medications. The most frequent medication was Kefzol as prophylaxis against endocarditis and other medications for heart failure or airway infection.

Premedication was received by all patients at center 1 and all but 7 patients at center 2 (4 VIS group and 3 OMN group). The most frequent premedications were ketamine, midazolam, Dolantine, and Phenergan.

Post-procedural medication - Fourteen patients (11 VIS, and 3 OMN) received post-procedural medications. The most common medications were Lasix, Lanoxin and blood transfusion. In the other cases, medication was given for different reasons, such as headache, pain after puncture, vomiting and heart disease.

Injection Information:

Phase-2: The mean total volume of VIS-320 mgI/mL was given 42,0 mL = 13.4 gI or 1.32 gI/kg bw (4.1 mL/kg bw). and the dose ranging from Eight of the patients had an injection in the LV, with the dose ranging from per injection. Five patients had an injection in the right ventricle. The other injections were performed in the aorta and pulmonary arteries.

Phase-3: (ref. Table 5a.II. p113, combined center 1 and center 2) - The mean volume of VIS-320 mgI/mL was given 52.5 mL =16.8 gI or 1.38 gI/kg bw (4.3 mL/kg bw). OMN-350 mgI/mL was given 61.3 mL = 21.5 gI or 1.39 gI/kg bw (4.0 mL/kg bw). The maximum amount of gI/kg bw was given 3.57 gI (11.1 mL) in the VIS group and 2.72 gI (7.8 mL) with the OMN group. The difference in mean volume and gI/kg between the two groups seems to reflect the skewness in age distribution, since the volumes administered per kg bw. were similar for the two groups.

Phase-2 (Pilot Study)

Drug & Weight Group		Total (N)	Total Volume(mL) Mean	Min	Max	(n)	Total Dose Iodine(gI) Mean	Min	Max	(n)	Body Weight(kg) Mean	Min	Max	(n)
VIS-320	<7 kg	2	31.5			2	10.1			2	1.57			2
	7-10 "	3	34.3			3	11.0			3	1.46			3
	>10-20 "	4	47.5			4	15.2			4	1.17			4
	>20 "	1	64.0			1	20.5			1	0.96			1
	Total	10	42.0			10	13.4			10	1.32			10

Phase-3 (center 1)

Drug & Weight Group		Total (N)	Total Volume(mL) Mean	Min	Max	(n)	Total Dose Iodine(gI) Mean	Min	Max	(n)	Body Weight(kg) Mean	Min	Max	(n)
VIS-320	<7 kg	8	32.3			8	10.3			8	2.22			8
	7-10 "	7	46.9			7	15.0			7	1.72			7
	>10-20 "	12	52.1			12	16.7			12	1.13			12
	>20 "	7	106.4			7	34.1			7	1.29			7
	Total	14	57.5			34	18.4			34	1.54			34
OMN-350	<7 kg	3	34.7			3	12.1			3	2.26			3
	7-10 "	2	36.5			2	12.8			2	1.51			2
	>10-20 "	8	54.6			8	19.1			8	1.38			8
	>20 "	4	118.0			4	41.3			4	1.07			4
	Total	17	63.9			17	22.4			17	1.48			17
Phase-3 (center 2)														
VIS-320	<7 kg	7	17.7			7	5.7			7	1.05			7
	7-10 "	2	31.5			2	10.1			2	1.21			2
	>10-20 "	7	55.7			7	17.8			7	1.08			7
	>20 "	2	97.5			2	31.2			2	0.93			2
	Total	18	42.9			18	13.7			18	1.06			18
OMN-350	<7 kg	2	18.5			2	6.5			2	1.47			2
	7-10 "	1	32.0			1	11.2			1	1.53			1
	>10-20 "	3	76.7			3	26.8			3	1.57			3
	>20 "	3	70.0			3	24.5			3	0.65			3
	Total	9	56.6			9	19.8			9	1.24			9

Reviewer's Comment - The mean dose were somewhat higher at center-1 than at center-2 in both drug groups. The mean dose of VIS-320 was 1.54 gI/kg bw at center-1, and 1.06 gI/kg bw at center-2 versus 1.48 and 1.24 gI/kg bw for the OMN-350 group. The difference was also apparent in most of the separate weight groups. Which may be due to clinical indications between two centers (ref. Tables 5a. III-IV, p114-5).

Patient withdrawal - No patient at either center who received administered contrast agent was excluded or was withdrawn from the study.

Efficacy Results - The overall quality of radiographic visualization were graded as diagnostic (good/excellent) for both phase -2 and phase-3 (center 1 and center 2) drug groups.

Safety Results:

Vital Signs - Pulse rate and both systolic/diastolic blood pressures were measured immediately prior to and at 60, 120, and 180 seconds after the contrast administration.

Phase-2: Although some individual variation was noticed, there were no clinically significant trends in change from baseline value in any of the vital signs parameters following the administration contrast media at 60, 120, and 189 seconds time points. One patient (#09) experienced mild-moderate hypotension from A few patients had increases greater than 20 mmHg in blood pressures and 15 bpm in pulse rate. None of these patients had any clinical significance.

Phase-3: There were no clinically significant changes in vital signs parameters during the 24 hour observation period, One OMN patient (#119; 2 year-old) had an increased pulse rate from bpm after the contrast administration, with the explanation that the patient was very agitated. The maximum increases and decreases were similar magnitude in the two contrast agent groups.

Hemodynamics:

Phase-2: Both intravascular blood pressures (systolic/diastolic) were recorded immediately prior to and at 30, 60, and 120 seconds after the contrast administration. The mean systolic pressure was slightly increased after the LV injection, due to one patient (#08; 9 months old), who had increases from 92 to 115, 117, and 116 mmHg at 60, 120, and 180 minutes after the injection, respectively. No individual changes of greater than 20 mmHg in diastolic pressure were noted in any of the injections. The mean increase in end-diastolic pressure was small, followed by LV injection (ref. Tables 9a.1,& 9b.1, p191-2).

Phase-3: - Both intravascular blood pressures (systolic/diastolic) were recorded immediately prior to and at 30, 60, 120 and 180 seconds after the contrast administration.

Systolic Blood Pressure:

Aortic Injection - The mean change was maximally -0,5 mmHg at 30 seconds after injection in the VIS-320 group versus -5.2 mmHg, at 30 seconds after injection with OMN-350 group. At the other time points, mean changes were small in both drug groups. In the OMN group, however, the maximum change was decrease of 26 mmHg from (patient #140; 11 year-old), at 60 seconds after the contrast administration. No other patients had changes of greater than 20 mmHg seen.

Pulmonary Artery Injection - The mean change was maximally +2.0 mmHg at 30 seconds after injection of VIS-320 versus +2.4 mmHg at 120 seconds after injection with OMN-350 group. None of the patients had any changes greater than 20 mmHg in either drug group.

LV Injection - The mean change was maximally +3.2 mmHg at 30 seconds after injection of VIS-320 versus +2.2 mmHg at 120 seconds after injection with OMN-350 group. One patient in each drug group had an increase of >20 mmHg: (Patient #224, 5-month-old in the VIS-320 group had an increased of 24 mmHg from the baseline, and the other OMN-350 patient #122, 2-year-old, had an increased of 22-24 mmHg from the baseline value).

Reviewer's Comment - No disagreement with the sponsor's analysis.

Diastolic Blood Pressure:

Aortic Injection - The mean change was maximally -0,7 mmHg at 120 seconds after injection of VIS-320 versus -4.2 mmHg, at 30 seconds after injection with OMN-350 group.

Pulmonary Artery Injection - The mean changes in diastolic pressure were small in both drug groups; maximally +1.5 mmHg in the VIS-320 group versus +1.1 mmHg with the OMN-350 group. No patients had changes of greater than 20 mmHg in either group.

Reviewer's Comment - The sponsor concluded that the diastolic pressure decreases to a lesser degree in the VIS-320 than the OMN-350 group after injection via aorta. I disagree with the sponsor's interpretation; first, the sponsor compared the results between VIS-320 (30 secs) and OMN-350 (120 secs) time points which were inappropriate and misleading. Second, the sponsor failed to indicate that the mean diastolic blood pressure of VIS-230 went up +2.7 from baseline value at 180 secs time point, whereas the mean diastolic blood pressure in the OMN-350 group only -0.2 mmHg below the baseline value. As Table 9a. II. p196 (combined center 1 and center 2) presented below:

Injection Site	Contrast Agent (MgI/mL)	Time Interval	Values Before / After Mean	Min	Max
Aorta	VIS-320	Immed before Injection	51.2		
		30 sec after injection	0.4		
		60 " " "	0.2		
		120 " " "	0.7		
		180 " " "	2.7		
	OMN-350	Immed before Injection	59.3		
		30 sec after injection	-4.2		
		60 " " "	-1.5		
		120 " " "	-2.9		
		180 " " "	-0.2		

Left Ventricular End Diastolic Pressure (LVED):

The mean changes after LV injections were slight increases in both contrast agent groups, with a peak mean change of +2.1 mmHg, at one minute after injection in the VIS-320 group, and +2.0 mmHg at 2 minutes after injection with the OMN-350 group. Although, some of the patients had increases greater than 4 mmHg. and the relative frequencies were similar between two groups.

Reviewer's Comment - No statistically significant difference between the contrast agent groups was noted. However, the mean increased in LVED pressure was maximally +8.0 mmHg, at 5 minutes after injection, in the VIS-320 group (ref. Table 9a. 11. p200):

Injection Site	Contrast Agent (MgI/mL)	Time Interval	Values Before / After Mean	Min	Max
LV	VIS-320	Immed before Injection	12.1		
		30 sec after injection	1.3		
		60 " " "	2.1		
		120 " " "	1.6		
		180 " " "	0.3		
		5 minute " "	8.0		
	OMN-350	Immed before Injection	12.4		
		30 sec after injection	0.9		
		60 " " "	1.9		
		120 " " "	2.0		
		180 " " "	1.0		

Electrocardiography (ECG) Parameters

The ECG parameters (PQ interval, Qtc, RR interval, ST segment, T-wave amplitude and HR were measured prior to and at 15, 30, 60, 120, and 180 seconds after injection for each injection site and contrast agent group.

Phase-2, 3 study results - The mean changes were small in all ECG parameters, but none of these changes were clinical relevance.

Arrhythmias - The Arrhythimas were recorded according to type and number of occurrences per minute. The most frequently occurring events were premature ventricular contractions (PVC) and premature atrial contractions (PAC). The probable cause of the arrhythimas due to mechanical stimulation.

ARRHYTHMIAS AFTER INJECTION

	Phase-II VIS-320(N=10)	Phase-III (combined ctr,1 and ctr. 2) VIS-320(N=52)	OMN-350(N=26)
Injection Site			
Aorta group	0	0	1
Pulmonalis	0	1	1
Lt. Ventricle	2	7	4
Rt. Ventricle	1	6	0
	3(30%)	14(27%)	6(23%)

Reviewer's Comment - Electrocardiographic responses were similar from patients administered VIS-320 and patients administered OMN-350. Arrhythimas were recorded according to type and number of occurrences per minute. There were two types of arrhythmias observed premature ventricular contractions (PVC) and premature atrial contractions (PAC). The probable cause of arrhythmias may be related to mechanical stimulation (when the heart is catheterized and/or when a contrast injection is made).

Laboratory Parameters - There were no statistically significant differences between the VIS-320 and OMN-350 groups in these serum chemistries. Although some individual patients had increases greater than 40% of the reference range in LDH parameter with both drug groups, but the changes in mean values were small.. Serum creatinine, however, there was no significant difference between the two contrast agent groups with regard to the mean change from baseline value.

Reviewer's Comment - The responses of the drug groups were similar with regard to chemistry parameters. There were no statistically or clinically significant differences between the two groups or changes from baseline at 24 hours. No trend was noted in patients who received either contrast agent.

Injection-Associated Discomfort - (Sponsor's description):

Phase-2: Due to their being sedated, none of of the patients were able to report injection-associated discomfort. Phase-3: Injection-associated discomfort was observed in 3 patients, all of them at Center-1, and all in the VIS-320 group. Eight (3 VIS-320 and 5 OMN-350) of the 78 patients were judged to be able to report injection-associated discomfort, all of them at Center-2. The remaining 70 patients were not able to report injection-associated discomfort due to age and/or sedation.

Adverse events other than injection-associated discomfort:

Phase-2: Only 4 of the 10 patients experienced 8 adverse events, none of which were considered to the drug related.

Phase-3: Ten patients experienced 26 adverse events in the VIS-320 group and five experienced 11 adverse events in the OMN-350 group; all events were recorded at Center-1. The most frequently occuring events were vomiting, headache, cough, & metabolic acidosis.

	Phase - 11				Phase - 111											
No.of Pts (10/78)	(4)				Center-1 (10/6)								Center-2 (0)			
Contrast Agent	VIS-320(10)				VIS-320				OMN-350				VIS-320				OMN-350			
ADRs	Mi	Mo	Se	Tot.	Mi	Mo	Se	Tot	Mi	Mo	Se	Tot	Mi	Mo	Se	Tot	Mi	Mo	Se	Tot
Cyanosis		1		1																
Hypotension		1		1																
Vomiting	3			3	3	1		4	3			3								
Abn. Crying									1			1								
Fever					2			2												
Leg Pain						1		1												
Pain									1			1								
Headache						1		1												
M. Acidosis					1			1												
Anemia					1			1												
Asphyxia					1			1												
Cough						1		1												
Arrhythmias			3					14				6								
Total			8					26				11								

Note: No adverse events occurred in the Center-2. It is hard to believe that no single adverse event occurred in the center-2 group.

Reviewer's Evaluation and Summary - This was a phase 11/111 (10 pilot patients were included in the noncomparative phase-2, whereas 78 patients, randomized into two (center-1 and center-2), clinical trial conducted in Belgium. There were no statistically significant differences in gender, age, weight or height between the two contrast agent groups. Except race was unevenly distributed. Ten patients (phase-2) received a mean volume of 42.0 mL or 1.32 gI/kg bw. Combined (center 1 and center 2) phase-3 trial; The mean volumes were 52.2 mL for VIS-320 mgI/mL or 1.38 gI/kg versus 61.3 mL with OMN-350 mgI/mL or 1.39 gI/kg bw. The mean dose of VIS-320 was 1.54 gI/kg bw at center-1, and 1.06 gI/kg bw at center-2 versus 1.48 gI/kg, and 1.24 gI/kg for the OMN-350 group. The difference was also apparent in most of the separate weight groups. Which may be due to clinical indications between two centers.

Efficacy Profile:

The overall quality of radiographic visualization were rated as diagnostic (good/excellent) for both phase-2 and phase-3 drug groups.

Safety Profile:

No life-threatening or serious adverse effects were encountered for any of the patients studied. There was no tabulation with respect to adverse event occurred in the center-2. The most frequently occurring adverse events were vomiting, fever, headache, hypotension & arrhythmias with mild to moderate intensity. Although clinically significant,transient individual changes were noted in vital signs, blood chemistry, hematology or physiological recordings for both drug groups after contrast administration, no medical intervention was required for these changes.

Reviewer's Comment:

The reviewer believes that the evidence suggests the claim that Visipaque-320 mgI/mL is comparable to Omnipaque-350 mgI/mL in safety and effectiveness.

APPEARS THIS WAY
ON ORIGINAL

Study Report (#1966)
Protocol #39998-011

U. S. CLINICAL CONTROLLED TRIAL
(PEDIATRIC CT OF THE HEAD)
PIVOTAL 1

Principal Investigators - List of Investigators and Patient Enrollment

Center	Name & Affiliation	Enrolled/Dosed
001	David Shrier, & Lena Ketonen, M. D. Univ. Of Rochester Hospital Rochester, NY	15/15
002	Charles Glasier, M. D. Arkansas Children's Hospital L.R. AR	9/9
004	Richard Towbin, M. D. Children's Hospital of Pittsburgh Pittsburgh, PA	17/17
005	Jordan Rosenblum, M. D. University of Chicago Hospital Chicago, IL	18/18
011	Thomas Slovis, M. D. Children's Hospital of Michiga Detroit, MI	12/12
012	Mary Edwards-Brown, M. D. JWR Hospital for Children Indianapolis, IN	4/4
Six Centers		75/75 Patients

Study Objectives:

To compare the efficacy of VIS-270 and VIS-320 mgI/mL and OMN-300 mgI/mL in pediatrtic patients requiring CT of the head by assessing the overall quality of the contrast enhancement, and assessing the diagnostic utility of the contrast medium.

To compare the safety of VIS-270 and VIS-320 mgI/mL and OMN-300 mgI/mL, in pediatrtic patients requiring CT of the head by assessing vital signs, laboratory parameters and adverse events.

Study Design:

This was a phase-3, multicenter, randomized, double-blind comparison of VIS-270, VIS-320, and OMN-300 in patients requiring CT scanning of the head. A total of 75 patients were enrolled. This study report consists of one protocol (39998-011) with a six different conters conducted under this protocol support the safety and efficacy of the drug. The demographic characteristic are as follows:

Demographic Characteristics	VIS-270 (N=23)	VIS - 320 (N=27)	OMN-300 (N=25)
Gender N (%)			
Male	14 (61)	16 (59)	19 (76)
Female	9 (19)	11 (41)	6 (24)
Age (yr)			
Mean (SD)	5.82 (3.75)	5.66 (3.46)	5.87 (4.06)
Range			
Weight (kg)			
Mean	23.20(14.10)	22.68(13.43)	25.23(16.09)
Range			
Height (cm)			
Mean	108.22(29.29)	106.59(28.83)	112.34(28.10)
Range			
Race (Cau/B/Other)	(11/11/1)	(12/13/2)	(13/11/1)

Reviewer's Comment - There were no statistically significant differences in gender, age, weight and race between the three contrast groups.

History of Sensitivity - Seventeen of the 75 patients had a history of sensitivity to medication and/or allergens: (includes 4 of 23 patients in the VIS-270 group, 7 of 27 patients in the 320 group and 6 of 25 patients in the OMN-300 group). The allergen sensitivities are; dust, pollen, grass and mild products.

High-Risk Factors - Patients may have reported more than one risk factor. The most frequently reported risk factors were asthma, sickle cell disease, hypertension, and renal disease.

Medications - Thirty-seven of the 75 patients who received one or more concurrent medications during 24 hours prior to CT scanning procedure. The most commonly medications received were CNS, alimentary tract, and systemic general antiinfective medications. The three groups were similar with regard to the use of concurrent medications. No patients received either steriod or antihistamine medications prior to the study procedure. The three groups were also similar with regard to the procedural medications (CNS, psycholeptics, and anesthetics).

Patient Withdrawals - No patient at either study center who received administered contrast agent was excluded or was withdrawn from the study.

Injection Information - All pediatric patients (75) received contrast agents only once. The mean volume of VIS-270 mgI/mL was 39.41mL = 10.64 gI = (0.47 gI/kg), for VIS-320 was given 44.60 = 14.27 gI (0.65 gI/kg), and versus 45.48 mL = 13.64 gI (0.55 gI/kg bw) for the OMN-300 mgI/mL. There were no statistically significant differences between contrast groups. The dosage of contrast agent administered was indicated by volume, total dose of iodine, and gI/kg bw as follows:

Summary of Dosing Information by Group
(stratified by age groups)

	VIS - 270			VIS - 320			OMN - 300		
Age groups(yr) No. of Patient	0 - <3 (N=6)	3 - <12 (N=17)	Total (N=23)	0 - <3 (N=7)	3 - <12 (N=20)	Total (N=17)	0 - <3 (N=7)	3 - <12 (N=18)	Total (N=25)
Dose (gI)									
Mean	**4.88**	**12.67**	**10.64**	**6.32**	**17.06**	**14.27**	**5.96**	**16.63**	**13.64**
Range									
Dose (gI/kg)									
Mean	**0.46**	**0.48**	**0.47**	**0.60**	**0.67**	**0.65**	**0.54**	**0.56**	**0.55**
Range									
Volume (mL)									
Mean	**18.08**	**46.94**	**39.41**	**19.74**	**53.30**	**44.60**	**19.86**	**55.44**	**45.48**
Range									

Reviewer's Comment - No disagreement with sponsor's analysis.

Efficacy Results - The overall radiographic quality of contrast enhancement was graded as adequate (good/excellent) for 96 to 100% of all patients. Only one patient in the VIS-320 group had non-diagnostic quality. The reference Table shown below. for the majority of patients in all groups, the contrast agent increased the diagnostic confidence was 91% in the VIS-270 group, 89% in the VIS-320 group and 88% for the OMN-300 group.

Summary of the Contribution of the Contrast Agent to the Ability
to Make a Radiographic Diagnosis, N(%)

Contribution of CM	VIS-270 (N=23)	VIS-320 (N=27)	OMN-300 (N=25)
Increased confidence in diagnosis	21 (91%)	24 (89%)	22 (88%)
Increased border definition	5 (22%)	2 (7%)	7 (28%)
Differential enhancement of a mass	1 (4%)	0	3 (12%)
Other	2 (9%)	1 (4%)	1 (4%)
N/Pts who had Additional diagnosis	5	0	7
Biopsy	-	-	2/2(100%)
Surgery	4/4(100%)	-	4/4(100%)
Additional imaging	3/3(100%)	-	5/5(100%)

Reviewer's Comment:

No disagreement with the sponsor's analysis. It seems that higher concentration contrast group do not yield any greater benefit in this clinical trial.

Safety Results:

Vital Signs - Both systolic/diastolic blood pressure and pulse rate were measured prior to and immediately after the scan, one hour and 16-32 hours post-contrast injection. There were more increases than decreases in both blood pressure and pulse rate across the three contrast groups. None of the changes in vital signs was considered to be clinically relevant change from baseline value. The scatterplots of post-injection vital sign versus baseline did not reveal any systematic shifts.

Laboratory Parameters - No apparent overall trends were noticed for any of the contrast agent groups in blood chemistry and hematology parameters. Although some individual variation was noticed, but no clinically relevant change observed. There were 7 patients in the VIS-270 group, 8 in the VIS-320 group and for 2 patients in the OMN-320 group that had abnormal laboratory results post-contrast injection. No patients in any contrast group had post-injection changes in serum creatinine that were >80% of the reference range.

Neurological Examination - The neurological examinations were performed (includes autonomic nervous system, coordination, cranial nerves, motor function, reflexes & sensory function). There were no clinically significant changes from baseline observed in the neurological parameters.

Adverse Events - There were no serious adverse effects encountered in the patients studied. Four of the 75 patients who experienced adverse events; (includes one in the VIS-270 group, 2 in the VIS-320 group and one in the OMN-300 group. All adverse events were mild in intensity, and all patients recovered within 24-hour observation time. Adverse events other than injection-associated discomfort presented in the Table below:

Number of Patient (4)	VIS-270 (N=1)			VIS-320 (N=2)			OMN-300 (N=1)		
Body As a Whole	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Pruritus					2				
Hemorrhage(surgical site)								1	
Nausea		1							
Vomiting		1							
Rash(maculopapular)					2				

Note: A patient may have had more than one kind of adverse event.

Reviewer's Comment:

The reviewer believe that the evidence supports the claims that Visipaque is comparble to Omnipaque in safety and effectiveness.

EUROPEAN CLINICAL CONTROLLED TRIAL
(PEDIATRIC CT OF THE HEAD)
PIVOTAL 2

Study Report (#2512)
Protocol #DXV039

Responsible Investigator: Bo Jacobsson, M. D., Ph.D
Department of Radiology
Ostra Sjukhuset
Gothenburg, Sweden

Sub-Investigators: Lars-Martin Wiklund, M. D., Ph.D
Same address as above

Knut Joachim Berg, M. D., Prof.
Renal Section, Medical Department
The National Hospital Oslo, Norway

Study Objectives - To assess and compare the safety and efficacy of VISIPAQUE and OMNIPAQUE in pediatric patients requiring CECT scanning of the head.

Study Design - This was a double-blind, parallel, randomized phase-3 comparison between VIS-270, and VIS-320 and OMN-300 mgI/mL drug groups. A total of 75 patients were enrolled. The demographic characteristics are as follows:

Demographic Characteristics		VIS-270 mgI/mL			VIS-320 mgI/mL			OMN-300 mgI/mL		
Total Patients. (N=75)		<2 yrs (3)	>2 yrs (22)	Total (25)	<2 yrs (1)	>2 yrs (24)	Total (25)	<2 yrs (3)	>2 yrs (22)	Total (25)
Gender (M/F)	38/37	1/2	10/12	11/14	0/1	15/9	15/10	0/3	12/10	12/13
Age (months)										
Mean	101.1	8.7	113.7	101.1	17.0	108.8	105.2	12.7	108.5	97.0
Min/Max										
Weight (kg)										
Mean	30.5	8.6	34.7	31.5	11.5	32.0	31.1	10.2	31.3	28.8
Min/Max										
Height (cm)										
Mean	127.9	70.7	133.1	125.6	81.0	134.1	132.0	76.7	133.0	126.2
Min/Max										
Race										
Caucasian	70	3	20	23	1	23	24	2	21	23
Black	2	0	1	1	0	1	1	0	0	0
Oriental	1	0	0	0	0	0	0	0	1	1
Other	1	0	0	0	0	0	0	1	0	1
Unknown	1	0	1	1	0	0	0	0	0	0
Total	75			25			25			25

Reviewer's Comment - There were no statistically significant differences in gender, age, weight or height between the contrast agent groups. However, race was unevenly distributed.

Medications - A total of 29 patients were premedicated and all except 2 patients were fully sedated; (8 patients in the VIS-270 group, 11 patients in the VIS-320 group and 10 patients in the OMN-300 mgI/mL group). All of them received sedatives.

Patient dropout/withdrawal - No patient dropped out or was withdrawn from the study. The drug code was not broken for any of the patients.

History of Risk Factors - Allergy and hypersensitivity were the most frequently seen (2 patients in the VIS-320 group and 4 patients in each of the other two contrast agent groups. There were four patients reported asthma; (2 patients in the VIS-320 group and one in each of the two other contrast agent groups).

Dosage Information - All patients received only one injection of contrast agent. The mean volume of the contrast agent for VIS-270 was given 89.1 mL=24.1 gI (0.78 gI/kg bw), for VIS-320 was 89.7 mL=28.7 gI (0.94 gI/kg bw) and the mean volume of 84.8 mL=25.4 gI (0.89 gI/kg bw) with the OMN-300 group see Table below):

Total Dosage Of Drug Injected Per Patient

No. of Patient	(N=75)	VIS - 270 (N=25)	VIS - 320 (N=25)	OMN - 300 (N=25)
Dose (gI)				
Mean	**(26.1)**	**24.1**	**28.7**	**25.4**
Range				
Dose (gI/kg)				
Mean	**(0.87)**	**0.78**	**0.94**	**0.89**
Range				
Volume (mL)				
Mean	**(87.9)**	**89.1**	**89.7**	**84.8**
Range				

Reviewer's Comment:

The previous dosage information was stratified by age groups, whereas in this Table presented information by dose per patient. How to combine this two study results by different format. There were no statistically significant differences between three contrast groups.

Efficacy Results:

The overall evaluation of radiographic quality were rated 100% diagnostic (excellent/good) for VIS-270 group, and VIS-320 group and 96% with the OMN-300 contrast groups.

Safety Results:

Vital Signs - Both systolic/diastolic blood pressure and pulse rate were measured prior to and immediately after the scan, and at end of the procedure. No clinically significant trends could be observed in mean changes from baseline value for any of the measurements. The scatterplots of post-injection vital sign versus baseline did not reveal any systematic shifts.

Laboratory Parameters - No laboratory parameters were measured in this clinical trial.

Neurological Examination - The neurological examination was not performed in this clinical trial.

Injection-Associated Discomfort - A total of none of 75 patients had injection-associated discomfort; (4 in the Vis-270 group, 3 in the VIS-320 group and 2 in the OMN-300 group). These events were all of mild intensity.

Adverse events other than injection-associated discomfort - There were no serious adverse effects encountered in the patients studied. All clinical adverse events and occurrences for this study site are shown in the following Table:

Number of Patient (8)	VIS-270 (N=4)			VIS-320 (N=2)			OMN-300 (N=2)		
Body As a Whole	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Tireness	1			1					
Nausea	2						1		
Vomiting									1
Erythema				1					
Urticaria	1								

Reviewer's Comment:

Despite of lack of laboratory measurements in this clinical trial, however, Reviewer believes the results of this study supports the claim that Visipaque is comparable to Omnipaque.

U.S. CLINICAL CONTROLLED TRIAL
(PEDIATRIC CT OF THE BODY)
PIVOTAL 1

Study Report (1967)
Protocol #39998-012

Principal Investigators - List of Investigators and Patient Enrollment

Center	Name & Affiliation	Enrolled/Dosed
001	Margery Manuli, M. D. Univ.of Rochester Hospital Rochester, NY	7/7
002	Deborah S. Ablin, M. D. Univ. Of CA Davis Med. Ctr Sacramento, CA	11/11
003	Mervyn Cohen, M.B., Ch.B. JWR Hospital for Children Indianapolis, IN	14/14
004	Donald Frush, M. D. Duke Medical Center Durham, NC	12/12
005	Jordan Rosenblum, M. D. University of Chicago Chicago, IL	11/11
025	Beverly Newman, M. D. Children's Hospital of Pittsburgh Pittsburg, PA	20/20
026	Thomas Slovis, M. D. Children's Hospital of Michigan Detroit, MI	4/4
Seven Centers		79/79 Patients

Study Objectives:

To compare the efficacy of VIS-270, and VIS-320 and OMN-300 in patients requiring CT scanning of the body, by measuring the overall quality of the contrast agent enhancement, obtaining a radiographic diagnosis, and assessing the diagnostic utility of the contrast agent.

To compare the safety of VIS-270, and VIS-320 and OMN-300, in pediatric patients requiring CT of the body, by measuring vital signs, laboratory parameters, injection-associated discomfort and adverse events.

Study Design - This was a phase-3, randomized, double-blind comparison of VIS-270 mgI/mL and VIS-320 mgI/mL and OMN-300 mgI/mL in pediatric patients requiring CT scanning of the body. A total of 79 pediatric patients (27 of these patients were enrolled in the OMN-300 group and the other two contrast agents were given to 26 pateints (see Table below).

Demographic Characteristics	VIS-270 (N=26)	VIS - 320 (N=26)	OMN-300 (N=27)
Gender N (%)			
Male	16 (62)	14 (54)	14 (52)
Female	10 (38)	12 (46)	13 (48)
Age (yr)			
Mean (SD)	5.19 (3.53)	4.87 (3.16)	5.56 (4.27)
Range			
Weight (kg)			
Mean	20.50(10.47)	18.84(11.36)	20.97 (15.83)
Range			
Height (cm)			
Mean	104.44(24.17)	102.32(21.45)	106.19(32.01)
Range			
Race (Cau/B/Oriental/Other)	(18/6/0/2)	(16/5/2/3)	(17/6/1/3)

Reviewer's Comment - There were no statistically significant differences in gender, age, and weight between the three contrast groups. However, race was unevenly distributed.

History of Sensitivity - Twenty-nine of the 79 pediatric patients had a history of sensitivity to medication and/or allergens: (includes 9 of 26 patients in the VIS-270 group, 11 of 26 patients in the 320 group and 9 of 27 patients in the OMN-300 group). The allergen sensitivities are; dust, food, and milk products.

High-Risk Factors - Patients may have reported more than one risk factor. The most frequently reported risk factors was renal disease. Liver disease, hypertension and asthma.

Medications:

Forty-eight of the 79 pediatric patients received one or more concurrent medications during the period from 24 hours prior to the CT scanning procedure until 16-32 hours post-contrast administration. The three groups were generally similar with regard to usage of concurrent medications. The most commonly received primary medications were systemic anti-infective medications, alimentary tract, and metabolism medications.

Thirty-three of the 79 patients received one or more procedural medications during the CT scanning procedure. Across all 3 groups, the most commonly used medications were psycholeptics and anesthetics.

Patient Withdrawals - No patient dropped out or was withdrawn from the study.

Injection Information - The mean volume of VIS-270 mgI/mL was 39.41mL=10.64 gI (0.47 gI/kg), for VIS-320 was given 44.60=14.27 gI (0.65 gI/kg), and versus 45.48 mL=13.64 gI (0.55 gI/kg bw) for the OMN-300 mgI/mL. There were no statistically significant differences between contrast groups. The dosage of contrast agent administered was indicated by volume, total dose of iodine, and gI/kg bw as follows:

Summary of Dosing Information by Group
(stratified by age groups)

	VIS - 270			VIS - 320			OMN - 300		
Age groups(yr)	0 - <3	3 - <12	Total	0 - <3	3 - <12	Total	0 - <3	3 - <12	Total
No. of Patient	(N=10)	(N=16)	(N=26)	(N=9)	(N=17)	(N=26)	(N=12)	(N=15)	(N=27)
Dose (gI)									
Mean	6.10	12.59	10.09	8.36	12.76	11.24	5.65	17.16	12.04
Range									
Dose (gI/kg)									
Mean	0.50	0.50	0.50	0.67	0.58	0.61	0.56	0.60	0.58
Range									
Volume (mL)									
Mean	22.58	46.63	17.38	26.11	39.88	35.12	18.83	57.204	40.15
Range									

Efficacy Results - The overall radiographic quality of contrast enhancement was graded as adequate (good/excellent) for 92 to 100% of all patients. Only two patients in the VIS-320 group had non-diagnostic quality (92%). There were no statistically significant differences observed among the contrast agent groups. The investigators were asked if the constrast agent contributed to their ability to make a radiographic diagnosis. For the majority of patients in all drug groups, the contrast agent increased the diagnostic confidence in 85-96% in the VIS-270 group, 92% in the VIS-320 group and 96% in the OMN-300 group, and increased the border definition for 62% in the VIS-270 group, 65% in the VIS-320 group and 70% with the OMN-300 group (ref. Vol.22.Table 9.2C. P58).

Summary of the Contribution of the Contrast Agent to the Ability
to Make a Radiographic Diagnosis, N(%)

Contribution of CM	VIS-270 (N=26)	VIS-320 (N=26)	OMN-300 (N=27)
Increased confidence in diagnosis	22 (85%)	24 (92%)	26 (96%)
Increased border definition	16 (62%)	17 (65%)	19 (70%)
Differential enhancement of a mass	5 (19%)	2 (8%)	6 (22%)
Other	2 (8%)	3 (12%)	5 (19%)
Additional diagnostic information			
Biopsy	3/3	7/8	9/10
Surgery	9/9	9/10	9/9
Additional imaging	13/14	17/17	17/17
Other	1/1	2/2	1/1

Reviewer's Comment:

No disagreement with the sponsor's analysis. It seems that higher concentration contrast VIS-320 group do not yield any greater benefit in this clinical trial.

Safety Results:

Vital signs - Systolic/diastolic blood pressure and pulse rate were assessed at baseline (immediately prior to), immediately following the last scan, and one hour and approximately 16-32 hours post-contrast injection. Although, individual changes from baseline in vital sign parameters, no clinically significant change were observed. Scatterplots of post-injection vital signs versus baseline values did not show any systemic shifts or trends.

Laboratory parameters:

The majority of changes were no more than 40% of the reference range and these changes were not clinically significant. Overall, changes from baseline greater than 80% of the reference range were noted in one or more hematology parameters for 8 patients (2 in the VIS-270 group, 3 in the VIS-320 group and 3 in the OMN-300 group) and in one or more serum chemistry parameters for ten patients (4 in each Visipaque groups and 2 in the OMN-300 group). None of these changes were considered to be clinically meaningful. The scatterplots of post-injection versus baseline values for laboratory parameters showed sporadic individual changes from baseline were noted in serum potassium and monocytes. Serum creatinine values, however, were within normal range at all time points.

Deaths:

A 9 year-old Caucasian girl (003-0753 in the VIS-270 group) who underwent a contrast enhanced CT examination of the kidneys on May 5, 1995. A single dose of 50 mL (1.34 mL/kg) VIS-270 mgI/mL was administered without incident and the study completed uneventfully. During the examination, patient also received 5 mL of oral contrast agent (OMN-300 mgI/mL diluted to 300 mL) for the CT procedure. Approximately 3 days later, the patient developed pulmonary edema of unknown etiology and was admitted to the ICU for evaluation and treatment. On May 9th, patient underwent open renal biopsy and left thoracoscopy with biopsy of the left upper lobe. The pulmonary biopsy showed severe fibrosis (consistent with carmustine toxicity), foamy macrophages, & possibly evidence of a foreign body reaction. In spite of aggressive treatment with high steroids, fluid restriction and cardiovascular support, however, patient expired on May 11th.

Injection-Associated Discomfort:

There were five patients who experienced injection-associated discomfort; (3 patients in the VIS-320 group and 2 patients in the OMN-300 group), all discomfort were of mild intensity (pain, heat and cold) and lasted from 2 seconds to two minutes. None had any discomfort in the VIS-270 group.

Adverse events:

There were four patients (3 in the VIS-270 group and 1 in the OMN-320 group) who experienced adverse events with mild and moderate-severe intensity. None of the patients in the VIS-320 group had any adverse event.

Number of Patient (4)	VIS-270 (N=3)			VIS-320 (N=2)			OMN-300 (N=1)		
Adverse Events	Mild	Mod	Severe	Mild	Mod	Severe	Mild	Mod	Severe
Systolic hypotension		1							1
Shortness of breath	1								
Vomiting							1		
Pulmonary edema			1						
Pruritus	1								
Muscle contractions	1								

Reviewer's Comment:

I disagree with the sponsor's analysis. Pulmonary edema should be listed as adverse event (3 days post-contrast administration, probably delayed effect) instead of pulmonary fibrosis because this has no impact with contrast administration.

APPEARS THIS WAY
ON ORIGINAL

EUROPEAN CLINICAL CONTROLLED TRIAL
(PEDIATRIC CT OF THE BODY)
PIVOTAL 2

Study Report (#2511)
Protocol #DXV038

Principal Investigator: Bjarne Smevik, M. D.
Rikshospitalet
Department of Pediastric Radiology
Oslo, Norway

Sub-Investigators: Jostein Westvik, M. D.
Gunnar Stake, M. D.
Knut Joachim Berg, M. D.
same address as above

Study Objectives - The objective of the study was to compare Visipaque and Omnipaque regarding safety and efficacy in patients requiring CT scanning of the body. Safety profile was measured by means of recording vital signs, laboratory parameters, injection-associated discomfort and adverse events, whereas efficacy was assessed by evaluating the quality of overall diagnostic information obtained from the contrast-enhanced scans of the body.

Study Design - This was a phase-3, randomized, parallel, double-blind comparison between VIS-270 mgI/mL and VIS-320 mgI/mL and OMN-300 mgI/mL in pediatric patients requiring CT scanning of the body. A total of 67 pediatric patients were enrolled. The demographic characteristics are as follows:

Demographic Characteristics		VIS-270 mgI/mL			VIS-320 mgI/mL			OMN-300 mgI/mL		
Total Patients. (N=67)		<2 yrs (8)	>2 yrs (14)	Total (22)	<2 yrs (6)	>2 yrs (16)	Total (22)	<2 yrs (3)	>2 yrs (20)	Total (23)
Gender (M/F)	39/28	5/3	9/5	14/8	5/1	9/7	14/8	0/3	11/9	11/12
Age (months) Mean	59.5	7.9	85.9	57.5	10.5	76.1	58.2	12.0	70.1	62.5
Min/Max										
Weight (kg) Mean	19.3	7.9	25.3	18.9	9.2	22.3	18.7	10.0	21.3	19.9
Min/Max										
Height (cm) Mean	106.4	67.0	121.8	103.6	72.3	117.0	104.2	76.0	115.9	110.7
Min/Max										
Race										
Caucasian	65	8	14	22	5	15	20	3	20	23
Oriental	1	0	0	0	1	0	1	0	0	0
Other	1	0	0	0	0	1	1	0	0	0

Reviewer's Comment:

There were no statistically significant differences in gender, age, and weight between the three contrast groups. However, race was unevenly distributed.

History of risk factors - Allergy and hypersensitivity were the types most frequently seen in eleven patients (one in the VIS-270 group, and 5 of patients in each of the other two groups). In addition, 3 patients reported asthma.

Medications - Twenty-seven patients were sedated and sedatives routinely used were Pentothal and/or Dormicum. In addition to sedatives atropine was given as pre-operative medication.

Patient Withdrawals - No patient dropped out or was withdrawn from the study.

Dosage Information - All patients received only one injection of contrast agent. The mean volume of the contrast agent for VIS-270 was given 37.9 mL=10.2 gI (0.54gI/kg bw), for VIS-320 was 37.4 mL=12.0 gI (0.64 gI/kg bw) and the mean volume of 39.2 mL=11.8 gI (0.59 gI/kg bw) with the OMN-300 group (see Table below):

Total Dosage Of Drug Injected Per Patient

No. of Patient	(N=69)	VIS - 270 (N=22)	VIS - 320 (N=22)	OMN - 300 (N=23)
Dose (gI)				
Mean	11.3	10.2	12.0	11.8
Range				
Dose (gI/kg)				
Mean	0.59	0.54	0.64	0.59
Range				
Volume (mL)				
Mean	38.2	37.9	37.4	39.2
Range				

Reviewer's Comment:

No disagreement with the sponsor's analysis. The volume of contrast agent injected were similar in all three groups. However, due to the different iodine concentrations of the three contrast agents (gI/kg bw), were somewhat different. The mean dose of iodine was lowest for patients in the VIS-270 group, whereas the highest dosage with the VIS 320 mgI/mL group.

Efficacy Results:

The overall quality of the contrast-enhanced CT images was rated as adequate (100%) for both VIS-270 and VIS-320 groups and 96% in the OMN-300 group. There were no statistically significant differences between drug groups.

Safety Results:

Vital signs - Both systolic/diastolic blood pressure and pulse rate were measured immediately prior to and at 30 minutes post-contrast administered. Vital sign changes in the present series were minor and of no obvious clinical importance in either contrast agent group.

Laboratory parameters:

Serum and urine samples were obtained from 24 (8 patients per each contrast group) of the 67 patients. None of the changes in serum chemistry, hematology and urine parameters were analysed by the clinical-chemistry-laboratory. In general, there were no clinically significant relevant change noted. Two patients (#011, #104) had no baseline urine sample obtained.

Adverse Events:

With respect to drug tolerance, no life-threatening or serious adverse effects were encountered in the patients studied. There were five patients (2 in the VIS-270 group, 1 in the VIS-320 group, and 2 in the OMN-300 group) who experienced 9 adverse events with mild-moderate in intensity (see Table below):

Number of Patient (5)	VIS-270 (N=2)				VIS-320 (N=1)				OMN-300 (N=2)			
Adverse Events	Mi	Mod	Sev	Tot.	Mi	Mod	Sev	Tot.	Mi	Mod	Sev	Tot.
Warmth feeling									1			1
Nausea						1		1		1		1
Vomiting						1		1		1		1
Exanthema		1		1								
Itching (pruitus)						1		1				
Sweating						1		1				
Taste perversion	1			1								
Total occurrences				2				4				3

Reviewer's Comment:

Despite the lack of laboratory measurements in this clinical trial, however, Reviewer believes the results of this study supports the claim that Visipaque is comparable to Omnipaque.